FDA Briefing Document

Joint Meeting of Anesthetic and Analgesic Drug Products Advisory Committee and Drug Safety and Risk Management Advisory Committee

September 10 2015

DISCLAIMER
STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought efficacy data, safety data, pharmacokinetic data, and results of studies evaluating the abuse of Avridi (oxycodone hydrochloride) immediate-release tablets to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

FOOD AND DRUG ADMINISTRATION

Center for Drug Evaluation and Research

Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee and Drug Safety & Risk Management Advisory Committee

September 10, 2015

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Division Director Memo

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND ADDICTION PRODUCTS

M E M O R A N D U M

DATE: August 14, 2015

FROM: Sharon Hertz, MD
Director
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II, CDER, FDA

TO: Chair, Members and Invited Guests
Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC)
Drug Safety and Risk Management Advisory Committee (DSaRM)

RE: Overview of the September 10, 2015 AADPAC/DSaRM Meeting to Discuss NDA 206830

At this joint meeting of AADPAC and DSaRM, we will be discussing an application from Purdue Pharma for a new immediate-release formulation of oxycodone with the proposed trade name, Avridi, designed with properties intended to deter abuse of the product by the intravenous and intranasal routes. If approved, Avridi would be indicated for the management of pain severe enough to require an opioid analgesic and for which alternative options are inadequate.

The abuse of prescription opioid products is a growing public health problem in the United States, but it is of great importance to maintain the availability of opioid analgesics for the millions of patients in this country who suffer from pain. FDA has encouraged drug companies to develop opioid analgesics with properties intended to deter their abuse. The Agency has supported the development of novel formulations through multiple interactions with both the pharmaceutical industry and the academic community. In April, 2015 the Agency issued a final guidance to assist industry in the development of opioid drug products with abuse-deterrent properties. The "Guidance for Industry: Abuse-Deterrent Opioids," explains the Agency's current thinking regarding

studies that should be conducted to demonstrate that a given formulation has abuse-deterrent properties, makes recommendations about how those studies should be performed and evaluated, and discusses how to describe those studies and their implications in product labeling.

There are four approved ERLA products with abuse-deterrent properties described in their labels, OxyContin (oxycodone extended-release tablets), Targiniq (oxycodone and naloxone extended-release tablets), Embeda (morphine sulfate and naltrexone extended-release capsules), and Hysingla ER (hydrocodone extended-release tablets).

Initially, most manufacturers focused on developing abuse-deterrent formulations for extended-release/long-acting (ERLA) opioid analgesics. In general the amount of opioid in an ERLA product is greater than the amount found in IR formulations, and the extraction of the opioid or the defeat of the extended-release mechanism for the ERLA opioids results in greater amounts of drug available for abuse by varied routes of administration. However, IR opioids are abused as well, and the development of abuse-deterrent immediate-release formulations that can reduce abuse by oral, nasal, or intravenous routes of abuse is also an important public health goal.

The reason for bringing the NDA for Avridi to this advisory committee meeting is to discuss the results of pharmacokinetic studies evaluating the effect of food on the absorption of oxycodone from Avridi and the results of studies describing the abuse-deterrent properties, and to consider these data when determining the overall risk and benefit of this product. Pharmacokinetic studies have demonstrated that the absorption of oxycodone from Avridi can be substantially delayed in the presence of food, and this food effect may impact both efficacy and safety. The Applicant proposes to address this finding by labeling the product to be taken on an empty stomach. However, because this immediate-release product is intended to be dosed every 4 to 6 hours, patients may have difficulty finding a time window during which to take their medication, and may be unable to comply with the instructions.

Opioid analgesics are generally taken without regard to food, and it is not clear whether labeling would be sufficient to change long-standing behaviors of both prescribers and patients. All of these issues may result in patients taking Avridi without regard to food, leading to variability in systemic exposure to oxycodone, variable or delayed efficacy, and the possibility of taking extra doses that could lead to serious adverse events.

You will be asked to discuss the potential safety risks and effects on efficacy associated with the delayed absorption of oxycodone when Avridi is taken with food, and the feasibility of labeling as an effective means to mitigate potential risks. You will also be asked to consider whether the potential public health benefit of the product's abuse-

deterrent properties outweigh the risk to patients who are prescribed Avridi for the management of pain.

These are clearly difficult questions for which there are no easy answers. We are asking that you provide your expertise, your experience and your best insights in order to help us find a reasonable and responsible path forward. Your advice and recommendations will be essential in assisting us with addressing this complex and critical public health concern. We are grateful that you have agreed to join us for this important discussion and look forward to seeing you at the meeting.

Draft Points to Consider

NDA 206830 Avridi (Oxycodone IR)

1. Discuss whether the pharmacokinetic data presented support a significant food effect resulting in marked delay in absorption and time to peak plasma concentration when this product is taken with food. Discuss the impact of this effect on the efficacy and safety of this product.

2. The Applicant intends to address this food effect by labeling the product to be taken on an empty stomach. Discuss whether patients are likely to be able to comply with this requirement given that the product is to be dosed every 4 to 6 hours.

3. Discuss whether it appears from the data presented that the abuse-deterrent properties of Avridi support the likelihood that the drug product will have a meaningful effect on abuse.

4. Discuss whether the requirement that Avridi must be taken on an empty stomach and the safety and efficacy concerns that may result from taking it without regard to food intake outweigh the possible public health benefits from the abuse-deterrent properties.

5. Should Avridi be approved for marketing in the US?

Summary of NDA Efficacy and Safety Findings

Clinical Development Program

The Sponsor conducted the following studies to support this NDA submission:

Study	N	Study Design
OCI1001 N-blocked	120	Randomized, Cross-Over in Healthy Subjects to Assess PK & Abuse-Deterrent (AD) of different OCI IR Formulations
OCI1002 N-blocked	53	Randomized, Open-label, Single-Dose, 2-way Cross-over in Healthy Subjects to Determine Fasting Bioequivalence (BE) of OCI 15 mg to Roxicodone 15 mg
OCI1003 N-Blocked	55	Randomized, Open-label, Single-dose, 2-way Cross-over Study in Healthy Subjects to Determine Fed BE of OCI 15 mg to Roxicodone 15 mg
OCI1005 PK/PD abuse potential	36	Single-center, randomized, double-blind, Cross-over Study to Evaluate Abuse Potential, Pharmacokinetics (PK) and Safety of Crushed and IN IR Oxycodone tabs in Recreational Opioid Users with History of IN abuse
OCI1008 Safety and tolerability	48	Randomized, Double-blind, Multiple-Dose, Placebo-Controlled, Parallel-Group Study in Healthy Subjects to Assess Safety and Tolerability of Sodium Lauryl Sulfate Administered in OCI Placebo Tablets

N-blocked = Naltrexone blocked
OCI = Oxycodone immediate-release abuse-deterrent formulation, proposed trade name Avridi
IR = immediate-release
IN = Intranasal

Review of Efficacy

There were no efficacy studies conducted in support of NDA 206830 AVRIDI (immediate-release oxycodone) tablet. The Applicant has relied in part on the Agency's prior findings of safety and effectiveness for Roxicodone (immediate –release oxycodone hydrochloride) tablet which was approved by the Agency on August 31, 2000. Roxicodone is an opioid containing oxycodone HCL in tablet strengths of 15 and 30 mg

Review of Safety

The assessment of the safety of AVRIDI relies on the clinical data provided and the Agency's prior findings of safety for the referenced product, Roxicodone. The safety profile of AVRIDI was assessed in 264 healthy subjects across four clinical studies (OCI1001, OCI1002, OCI1003 and OCI1005). Subjects in Studies 1001, 1002, and 1003 were naltrexone-blocked, so the safety

data from these studies are of limited value. Overall in the studies where subjects were naltrexone blocked, the most common adverse events (AEs) reported were: nausea, vomiting and diarrhea. An additional clinical study (OCI1008) was conducted, however, no oxycodone was administered in this trial. This study evaluated the tolerability and safety of orally administered placebo tablets with and without the excipient, sodium laurel sulfate (SLS). The assessment of safety for AVRIDI relies on the data from Study OCI1005, a human abuse potential study evaluating the relative drug liking of intact orally administered AVRIDI, manipulated AVRIDI by nasal route of administration as compared to manipulated Roxicodone and placebo by the nasal route of administration, provided below.

Major Safety Results

There were no serious adverse events (including deaths) reported during clinical development of AVRIDI.

Overall, three subjects [were discontinued from studies because of treatment emergent adverse events (TEAEs), one for vomiting after administration of AVRIDI and two after administration of Roxicodone.

Table 1 is a summary of TEAEs that occurred in ≥5% of subjects exposed to AVRIDI by treatment group and system-organ-class (SOC) and preferred term (PT). In this table AVRIDI is referred to as OCI.

Table 1: TEAES Reported by ≥5% of Subjects (for Any Treatment) By Treatment at Onset and by System Organ Class and Preferred Term, Safety Population

MedDRA System Organ Class / Preferred Term	Number of Subjects (%)			
	Placebo (N=35)	Roxicodone 30 mg, crushed IN (N=35)	OCI 30 mg, crushed IN (N=35)	OCI 30 mg, intact oral (N=36)
Any System Organ Class				
Any event	10 (28.6)	21 (60.0)	32 (91.4)	22 (61.1)
Eye disorders				
Any event	1 (2.9)	2 (5.7)	29 (82.9)	0
Lacrimation increased	1 (2.9)	2 (5.7)	28 (80.0)	0
Ocular hyperaemia	0	0	7 (20.0)	0
Gastrointestinal disorders				
Any event	0	6 (17.1)	8 (22.9)	8 (22.2)
Eructation	0	0	2 (5.7)	0
Nausea	0	5 (14.3)	4 (11.4)	7 (19.4)
Vomiting	0	2 (5.7)	3 (8.6)	3 (8.3)
General disorders and administration site conditions				
Any event	0	2 (5.7)	4 (11.4)	3 (8.3)
Feeling hot	0	1 (2.9)	3 (8.6)	3 (8.3)
Nervous system disorders				
Any event	3 (8.6)	7 (20.0)	13 (37.1)	11 (30.6)
Dizziness	0	3 (8.6)	2 (5.7)	2 (5.6)
Headache	2 (5.7)	3 (8.6)	8 (22.9)	1 (2.8)
Somnolence	0	3 (8.6)	5 (14.3)	9 (25.0)
Tremor	0	0	2 (5.7)	0
Respiratory, thoracic and mediastinal disorders				
Any event	7 (20.0)	15 (42.9)	32 (91.4)	14 (38.9)
Cough	0	1 (2.9)	7 (20.0)	0
Dyspnoea	0	0	7 (20.0)	0
Intranasal paraesthesia	0	2 (5.7)	0	1 (2.8)
Nasal congestion	6 (17.1)	2 (5.7)	15 (42.9)	3 (8.3)
Nasal discomfort	2 (5.7)	10 (28.6)	22 (62.9)	11 (30.6)
Oropharyngeal pain	0	0	4 (11.4)	0
Rhinalgia	0	1 (2.9)	3 (8.6)	0
Rhinorrhoea	0	1 (2.9)	12 (34.3)	1 (2.8)
Throat irritation	1 (2.9)	1 (2.9)	15 (42.9)	0
Upper-airway cough syndrome	0	2 (5.7)	0	1 (2.8)
Skin and subcutaneous tissue disorders				
Any event	0	8 (22.9)	4 (11.4)	10 (27.8)
Pruritus	0	1 (2.9)	1 (2.9)	2 (5.6)
Pruritus generalised	0	8 (22.9)	3 (8.6)	8 (22.2)

Overall, the highest incidence of TEAEs was observed after administration of AVRIDI crushed intranasal () (91.4%), followed by AVRIDI intact oral (61.1%) Roxicodone crushed IN (60.0%) and the lowest following administration of placebo (28.6%).

Nasal discomfort was the most common TEAE reported among all treatment groups with the highest incidence being reported in the AVRIDI crushed IN treatment group.

Other common reported AEs in the AVRIDI crushed IN treatment group included: nasal congestion, throat irritation, rhinorrhea, cough, dyspnea, somnolence, generalized pruritus, lacrimation increased and ocular hyperemia,

In summary, subjects who received crushed AVRIDI 30 mg IN reported substantially higher percentages of nasal and/or oropharyngeal adverse events compared to subjects who received crushed Roxicodone 30 mg IN, intact AVRIDI 30 mg orally or placebo. The adverse events reported in the crushed AVRIDI 30 mg IN treatment group were not unexpected due to the presence of the SLS excipient in AVRIDI.

Background Document:

Abuse-Deterrent Immediate-Release Opioid Analgesics

The abuse of prescription opioid products is a growing public health problem in the United States. In light of this, the Agency has encouraged drug companies to develop novel analgesics, including new opioid analgesic formulations with abuse-deterrent properties to deter abuse, while recognizing the importance of maintaining the availability of opioid analgesic products for the millions of patients in this country who suffer from chronic pain. The Agency has supported the development of novel opioid formulations through multiple interactions with both the pharmaceutical industry and the academic community.

In April, 2015 the Agency issued a final guidance to assist industry in the development of opioid drug products with potentially abuse-deterrent properties. The "Guidance for Industry: Abuse-Deterrent Opioids," explains the Agency's current thinking regarding studies that should be conducted to demonstrate that a given formulation has abuse-deterrent properties, makes recommendations about how those studies should be performed and evaluated, and discusses how to describe those studies and their implications in product labeling. It is important to keep in mind that that the science of abuse deterrence is relatively new, and both the formulation technologies and the analytical, clinical, and statistical methods for evaluating those technologies are rapidly evolving. Based on this, the Agency intends to take a flexible, adaptive approach to the evaluation and labeling of potentially abuse-deterrent products.

Until recently, most sponsors have focused on the development of abuse-deterrent opioid formulations for extended-release/long-acting (ERLA) opioid analgesics. In general the amount of opioid in an ERLA product is greater than the amount found in IR formulations, and the extraction of the opioid or the defeat of the extended-release mechanism for the ERLA opioids results in greater amounts of drug available for abuse by various routes of administration. However, IR opioids are abused as well, and the development of AD formulations for these products is also an important public health goal.

At present, there are four approved products, all extended-release formulations, with abuse-deterrent properties described in their labels, OxyContin (oxycodone extended-release tablets), Targiniq (oxycodone and naloxone extended-release tablets), Embeda (morphine sulfate and naltrexone extended-release capsules), and Hysingla ER (hydrocodone extended-release tablets).

It is important to recognize that abuse-deterrent opioid products are not abuse proof. As stated in the “Guidance for Industry: Abuse-Deterrent Opioids, “Because opioid products are often manipulated for the purposes of abuse by different routes of administration or to defeat extended-release (ER) properties, most abuse-deterrent technologies developed to date are intended to make manipulation more difficult or to make abuse of the manipulated product less attractive or les rewarding. It should be noted that these technologies have not yet proven successful at deterring the most common form of abuse - swallowing a number of intact capsules or tablets to achieve a feeling of euphoria. Moreover, the fact that a product has abuse-deterrent properties does not mean that there is no risk of abuse. It means rather, that the risk of abuse is lower than it would be without such properties. Because opioid products must in the end be able to deliver the opioid to the patient, there may always be some abuse of these products.”

Similar to the abuse-deterrent ERLA products, IR products with abuse-deterrent properties are required to conduct postmarketing epidemiologic studies to determine whether the marketing of a product with abuse-deterrent properties results in meaningful reductions in abuse, misuse, and related adverse clinical outcomes, including addiction, overdose and death in the post-approval setting.

Abuse-Deterrent Opioids — Evaluation and Labeling

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

Clinical Medical
April 2015

Abuse-Deterrent Opioids — Evaluation and Labeling

Guidance for Industry

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Abuse-Deterrent Opioids — Evaluation and Labeling Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not create any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance explains FDA's current thinking about the studies that should be conducted to demonstrate that a given formulation has abuse-deterrent properties. The guidance makes recommendations about how those studies should be performed and evaluated and discusses how to describe those studies and their implications in product labeling.

This guidance is intended to assist sponsors who wish to develop opioid drug products with potentially abuse-deterrent properties and is not intended to apply to products that are not opioids or opioid products that do not have the potential for abuse.

This guidance also does not address issues associated with the development or testing of generic formulations of abuse-deterrent opioid products. FDA intends to address that topic in one or more future guidance documents.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Prescription opioid products are an important component of modern pain management. However, abuse and misuse of these products have created a serious and growing public health problem. One potentially important step towards the goal of creating safer opioid analgesics has

[1] This guidance has been prepared by the Division of Anesthesia, Analgesia, and Addiction Products, the Office of Regulatory Policy, the Office of Surveillance and Epidemiology, the Office of Biostatistics, and the Controlled Substance Staff in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

been the development of opioids that are formulated to deter abuse. FDA considers the development of these products a high public health priority.

Because opioid products are often manipulated for purposes of abuse by different routes of administration or to defeat extended-release (ER) properties, most abuse-deterrent technologies developed to date are intended to make manipulation more difficult or to make abuse of the manipulated product less attractive or less rewarding. It should be noted that these technologies have not yet proven successful at deterring the most common form of abuse—swallowing a number of intact capsules or tablets to achieve a feeling of euphoria. Moreover, the fact that a product has abuse-deterrent properties does not mean that there is no risk of abuse. It means, rather, that the risk of abuse is lower than it would be without such properties. Because opioid products must in the end be able to deliver the opioid to the patient, there may always be some abuse of these products.

For purposes of this guidance, *abuse-deterrent properties* are defined as those properties shown to meaningfully ***deter*** abuse, even if they do not fully ***prevent*** abuse. The term *abuse* is defined as the intentional, non-therapeutic use of a drug product or substance, even once, to achieve a desirable psychological or physiological effect.[2] Abuse is not the same as *misuse*, which refers to the intentional therapeutic use of a drug product in an inappropriate way and specifically excludes the definition of abuse.[3] This guidance uses the term *abuse-deterrent* rather than *tamper-resistant* because the latter term refers to, or is used in connection with, packaging requirements applicable to certain classes of drugs, devices, and cosmetics.[4]

The science of abuse deterrence is relatively new, and both the formulation technologies and the analytical, clinical, and statistical methods for evaluating those technologies are rapidly evolving. Based on the evolving nature of the field, FDA intends to take a flexible, adaptive approach to the evaluation and labeling of potentially abuse-deterrent products. Methods for evaluating the abuse-deterrent properties of new molecular entities may have to be adapted based on the characteristics of those products and the anticipated routes of abuse. The development of an abuse-deterrent opioid product should be guided by the need to reduce the abuse known or expected to occur with similar products.

Because FDA expects that the market will foster iterative improvements in products with abuse-deterrent properties, no absolute magnitude of effect can be set for establishing abuse-deterrent characteristics. As a result, FDA intends to consider the *totality of the evidence* when reviewing the results of studies evaluating the abuse-deterrent properties of a product.

[2] Smith S M, Dart R C, Katz N P, et al. 2013. Classification and definition of misuse, abuse, and related events in clinical trials: ACTTION systematic review and recommendations. *Pain,* 154:2287-2296.

[3] Ibid.

[4] FDA's current Good Manufacturing Practice regulations include tamper-evident packaging requirements. See 21 CFR 211.132. There are also requirements for child resistant "special packaging" under the Poison Prevention Packaging Act and regulations adopted by the Consumer Protect Safety Commissioner (CPSC) in 16 CFR 1700.

As with all NDA products, FDA intends to consider opioids with abuse-deterrent properties within the context of available therapy. The standard against which each product's abuse-deterrent properties are evaluated will depend on the range of abuse-deterrent and non-abuse-deterrent products on the market at the time of that application.[5]

Abuse-deterrent properties can generally be established only through comparison to another product.

FDA encourages additional scientific and clinical research that will advance the development and assessment of abuse-deterrent technologies.

FDA believes it is critical to address the problem of opioid abuse while seeking to ensure that patients in pain have appropriate access to opioid products. Moreover, it is important that opioids without abuse-deterrent properties remain available for use in some clinical settings. For example, patients in hospice care and with difficulty swallowing may need access to opioid products that are in solution or that can be crushed.

The following section describes the categories of abuse-deterrent products. The premarket and postmarket studies that should be performed to assess the impact of a potentially abuse-deterrent product are discussed in subsequent sections. Finally, information is provided about labeling for abuse-deterrent products.

III. ABUSE-DETERRENT PRODUCTS

Opioid products can be abused in a number of ways. For example, they can be swallowed whole, crushed and swallowed, crushed and snorted, crushed and smoked, or crushed, dissolved and injected. Abuse-deterrent technologies should target known or expected routes of abuse relevant to the proposed product. As a general framework, abuse-deterrent formulations can currently be categorized as follows:

1. *Physical/chemical barriers* – Physical barriers can prevent chewing, crushing, cutting, grating, or grinding of the dosage form. Chemical barriers, such as gelling agents, can resist extraction of the opioid using common solvents like water, simulated biological media, alcohol, or other organic solvents. Physical and chemical barriers can limit drug release following mechanical manipulation, or change the physical form of a drug, rendering it less amenable to abuse.
2. *Agonist/antagonist combinations* – An opioid antagonist can be added to interfere with, reduce, or defeat the euphoria associated with abuse. The antagonist can be sequestered and released only upon manipulation of the product. For example, a drug product can be

[5] For guidance on the evaluation of abuse potential for purposes of the Controlled Substances Act (CSA), we refer sponsors to FDA's draft guidance for industry *Assessment of Abuse Potential of Drugs*. This guidance is available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf. FDA guidances are available at http://www.fda.gov/RegulatoryInformation/Guidances/default htm.

formulated such that the substance that acts as an antagonist is not clinically active when the product is swallowed, but becomes active if the product is crushed and injected or snorted.

3. *Aversion* – Substances can be added to the product to produce an unpleasant effect if the dosage form is manipulated or is used at a higher dosage than directed. For example, the formulation can include a substance irritating to the nasal mucosa if ground and snorted.
4. *Delivery System* (including use of depot injectable formulations and implants) – Certain drug release designs or the method of drug delivery can offer resistance to abuse. For example, sustained-release depot injectable formulation or a subcutaneous implant may be difficult to manipulate.
5. *New molecular entities and prodrugs*– The properties of a new molecular entity (NME) or prodrug could include the need for enzymatic activation, different receptor binding profiles, slower penetration into the central nervous system, or other novel effects. Prodrugs with abuse-deterrent properties could provide a chemical barrier to the in vitro conversion to the parent opioid, which may deter the abuse of the parent opioid. New molecular entities and prodrugs are subject to evaluation of abuse potential for purposes of the Controlled Substances Act (CSA).
6. *Combination* – Two or more of the above methods could be combined to deter abuse.
7. *Novel approaches* – This category encompasses novel approaches or technologies that are not captured in the previous categories.

IV. PREMARKET STUDIES

First and foremost, any studies designed to evaluate the abuse-deterrent characteristics of an opioid formulation should be scientifically rigorous. Important general considerations for the design of these studies include the appropriateness of positive controls[6] and comparator drugs, outcome measures, data analyses to permit a meaningful statistical analysis, and selection of subjects for the study.

The evaluation of an abuse-deterrent formulation should take into consideration the known routes of abuse for the non-abuse-deterrent predecessor or similar products, as well as anticipate the effect that deterring abuse by one route may have on shifting abuse to other, possibly riskier route. For example, if a product is known to be abused using nasal and intravenous routes, developing deterrent properties for the nasal route in the absence of deterrent properties for the intravenous route risks shifting abusers from the nasal to the intravenous route, which is associated with a greater risk for the spread of infectious diseases.

Another concept that should be considered is whether the deterrent effects can be expected to have a meaningful impact on the overall abuse of the product. For example, immediate-release (IR) opioid and acetaminophen combination products are predominantly abused using the oral

[6] For purposes of this guidance, a positive control is an opioid drug product or drug substance expected to result in a predictable opioid drug liking effect and has a known potential for, or history of, abuse.

route. Demonstrating a deterrent effect by the nasal route may not meaningfully reduce overall abuse of the product.

FDA is committed to retaining a flexible, adaptive approach to evaluating potentially abuse-deterrent opioid drug products. This flexibility is intended to permit a sponsor to tailor the development program to suit the abuse-deterrent characteristics of their product and the routes of abuse for that product. The adaptive aspect is intended to permit a sponsor to take into consideration the relevant products on the market at the time they are developing their product, so that appropriate non-abuse-deterrent and abuse-deterrent comparators can be used. For example, for some proposed products the appropriate comparator may be a conventional formulation. However, if there are similar approved products with abuse-deterrent properties described in labeling, the appropriate comparator should be one of those abuse-deterrent products.

The following sections describe three categories of premarket studies. Although, in general, any development program for studying abuse-deterrent technologies should include data from all three categories of studies, there may be exceptions. For example, a formulation with a sequestered antagonist may intentionally be formulated not to resist crushing, so testing the syringeability of the product may not be relevant. In most cases, however, to obtain a full and scientifically rigorous understanding of the impact of a technology or technologies on a product's abuse potential, data from each of the following three categories of premarket studies are appropriate:

1. Laboratory-based in vitro manipulation and extraction studies (Category 1)
2. Pharmacokinetic studies (Category 2)
3. Clinical abuse potential studies (Category 3)

The results of Category 1 studies may influence the design of Category 2 pharmacokinetic studies and Category 3 clinical abuse potential studies by suggesting the methods of manipulation that would yield the greatest release of opioid. The results of Category 2 studies may influence the need for Category 3 studies of clinical abuse potential and the designs and goals of these studies. For example, if the extended-release characteristics of an abuse-deterrent opioid formulation cannot be defeated and the pharmacokinetic profile remains unchanged following oral or nasal administration of the manipulated product, oral and nasal studies of abuse potential may not be necessary.

Additional studies (i.e., Category 4 studies) analyze postmarket data to assess the impact of an abuse-deterrent formulation on actual abuse. Nonclinical drug discrimination studies are useful in the evaluation of the abuse potential of a drug, but their utility in predicting the impact of abuse-deterrent properties on human behavior has not been established.[7]

[7] See FDA draft guidance for industry, *Assessment of Abuse Potential of Drugs* see http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm198650.pdf.

A. Laboratory Manipulation and Extraction Studies (Category 1)

The goal of laboratory-based Category 1 studies should be to evaluate the ease with which the potentially abuse-deterrent properties of a formulation can be defeated or compromised. This information should be used when designing Category 2 and Category 3 studies. These studies are critical to the understanding of product characteristics and performance.[8]

Methodologically, these studies should be designed with knowledge of the physicochemical properties of the product and the methods available to abusers to manipulate the product and should be conducted on the to-be-marketed formulation. Sponsors should consider both the mechanisms by which abusers can be expected to attempt to deliberately overcome the abuse-deterrent properties of the product as well as the ways that patients may alter the formulation (unintentionally or intentionally) that change the rate or amount of drug released (e.g., dose dumping may occur when taking the product with alcohol or when the product is cut, chewed, or crushed). Testing should provide information sufficient to fully characterize the product's abuse-deterrent properties, including the degree of effort required to bypass or defeat those properties. In some cases, when designing in vitro studies, it may be useful to obtain information from prescription opioid abusers about how they would manipulate and abuse an abuse-deterrent product.

In vitro studies should assess various simple and sophisticated mechanical and chemical ways a drug could be manipulated, such as by (1) defeating or compromising the controlled release of an opioid from ER formulations for purposes of abuse by different routes of administration; (2) preparing an IR formulation for alternative routes of administration; or (3) separating the opioid antagonist, if present, from the opioid agonist, thus compromising the product's abuse-deterrent properties. The goal of these studies is to manipulate the product to the point of defeating its abuse-deterrent properties. Once this goal is achieved, it is no longer necessary to continue experiments using more sophisticated methods. For example, if 90% of the opioid can be extracted under a set of conditions in 10 minutes, there is no need to test the same condition for 30 minutes.

The test product should be compared to appropriate comparator products for ease of mechanical manipulation. The ability to crush, cut, grate, or grind the product formulation using readily available items such as spoons, cutters, and coffee grinders should be assessed. Particular attention should be given to particle size distribution following each mode of physical manipulation because particle size may influence the rate of opioid extraction from manipulated product. The effect of heat and cold on mechanical manipulation should also be studied.

Extractability and solubility studies should be designed to determine whether any of the formulation components might be differentially solubilized and extracted, allowing an abuser to

[8] This topic has been discussed at meetings of the Anesthetic & Life Support Drugs Advisory Committee and the Drug Safety & Risk Management Advisory Committee (*NDA 022272, OxyContin*, May 5, 2008, and September 24, 2009). Additional information on these meetings is available on FDA's web site at the following location: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM187082.pdf.

bypass the drug's abuse-deterrent properties. In addition to extraction and solubility studies, an assessment should be made to determine if free-base opioid can be precipitated from solution by pH adjustment. After establishing how a product could be manipulated, chemical extraction of the opioid from the intact and the manipulated product should be assessed and compared to opioid extraction from the selected intact and similarly manipulated comparator products.

The ease of extracting the opioid from the intact and manipulated product should be determined using a variety of solvents that are commonly available (e.g., water, vinegar, ethanol, isopropanol, acetone, mineral spirits) and those that have potentially relevant solvent characteristics (e.g., pH, polarity, protic vs. aprotic). The effects of time, temperature, pH, and agitation on solvent extraction should also be determined. For products containing more than one drug substance, extractability and solubility studies should be designed to determine whether any of the active ingredients might be differentially solubilized and extracted. Sampling times should start early (e.g., 30 seconds) and continue until at least 80% of the opioid has been released, or 12 hours has been reached. The in vitro drug-release characteristics of the intact and manipulated product should also be compared using a discriminatory and robust dissolution method.

In addition to the general evaluation of the effects of physical and chemical manipulation on the product, there are important route-specific data that should be generated, as follows:

- For a product with potential for abuse by the nasal route, the particle size distribution following attempted manipulation by various methods should be established, and the method that provides the smallest particle size should be used in subsequent studies.

- For a product with potential for abuse by smoking, the amount of drug produced by vaporization at temperatures encompassing the range from the melting point of the active ingredient to its degradation point should be determined. Appropriate controls, such as pure active ingredient, both in salt and free-base form should be included in these assessments.

- For a product with potential for abuse by injection, the amount of opioid that can be obtained in a syringe should be based on studies of intact and manipulated test product and comparator(s) using small volumes of water (5-10 mL) at room temperature and at 90° C – 95° C with and without agitation. Extraction times should range from 30 seconds to 30 minutes. The amount of opioid extracted, the volume of solution collected and the viscosity of the samples should be recorded. The ability to get the sample into a syringe and expel the sample using needles of various gauges should also be explored.

The following examples illustrate the kinds of outcomes that in vitro studies should evaluate.

1. Characteristics of the product by crushing, grinding or melting, or by changing the intact formulation using other methods that would limit nasal administration of the manipulated product, and/or that would limit dissolution of the manipulated product and incorporation into a solvent that could then be injected by intravenous or subcutaneous routes.

2. Quantity of the opioid extracted from the product following the various methods attempted that could be used for injection by intravenous or subcutaneous routes and a description of any barriers resulting from attempts at dissolution for drawing the drug into a syringe.

3. Quantity of opioid antagonist released from an agonist/antagonist combination when it is manipulated for administration by ingestion, nasal administration, or injection.

4. Quantity of opioid product following in vitro manipulation of the prodrug.

B. Pharmacokinetic Studies (Category 2)

The goal of the clinical pharmacokinetic studies, Category 2, should be to understand the in vivo properties of the formulation by comparing the pharmacokinetic profiles of the manipulated formulation with the intact formulation and with manipulated and intact formulations of the comparator drugs through one or more routes of administration. Even though the same routes of administration should be studied for the new product and comparators, if specific circumstances prevent this approach, the study design should be discussed with FDA. The method of manipulation used for the pharmacokinetic studies should be based on the methods explored during in vitro testing that can be expected to result in the greatest drug release. The routes of administration chosen should be relevant to the proposed product, and likely will be based on what is known about the abuse of similar products. Note that, for some development programs, it may be preferable to combine measures of pharmacokinetic parameters for Category 3 studies, in which case separate Category 2 studies may not be necessary.

In general, the pharmacokinetic profile for the oral route of administration should be studied. Appropriate study subjects for Category 2 studies include healthy volunteers as long as naltrexone is used to block the pharmacodynamic effects of the opioids.

Depending on the product, it may be important to evaluate the pharmacokinetic profile for the nasal route of administration as well. For nasal pharmacokinetic studies, it is important to weigh the risk to the subject based on the excipients in the formulation. Only subjects with a history of nasal abuse of opioids should be recruited for these studies. As with the oral route of administration, it may be possible to combine the pharmacokinetic assessment and the pharmacodynamic assessment in one clinical abuse potential study with sampling for the pharmacokinetic analysis.

Relevant pharmacokinetic parameters for the opioid drug and any psychoactive metabolites that should be measured in these studies include the following.

- Maximum concentration (C_{max})
- Time to maximum concentration (T_{max})
- Area under the curve (AUC_{0-t} and $AUC_{0-\infty}$)
- Relevant partial AUC, including early time points such as AUC_{0-30} minutes or AUC_{0-2} hours, the period of time when Cmax is expected
- Terminal elimination half-life ($T_{1/2}$)

Traditional pharmacokinetic study designs should be employed (e.g., crossover designs), and the results should be analyzed using bioequivalence methods. The rate of rise of drug concentration should be assessed when possible because it is thought to contribute to differential abuse potential among drugs, formulations, and routes of administration.[9] To support these analyses, it is important to have specimen collection and analysis time points sufficient to cover the onset, peak, and offset of the effects of both IR and ER formulations, in both the intact and manipulated conditions. In addition, these data are necessary to calculate the relevant partial area under the curve, which should capture the time to maximum concentration of the opioid.

If food and alcohol alter the pharmacokinetic parameters of the formulation, data should be provided to characterize those effects.[10] If food significantly increases systemic exposure of the intact formulation, the underlying mechanism for the food effect should be established by assessing whether the effect is based on the drug substance or the formulation and whether the effect is present with intact product as well as with manipulated product. When food is expected to increase exposure, subsequent abuse potential studies of the oral route should be conducted in the fed state to maximize the potential systemic exposure.

In addition to the pharmacokinetic profile of the opioid, for agonist/antagonist combinations , the pharmacokinetic characteristics of the antagonist should be defined for the intact product as well as for the manipulated formulation.

As with all clinical studies, adverse events should be collected, and those that can provide additional insight about the abuse-deterrent effects are especially important. For example, if the manipulated formulation is abused by snorting, it would be important to assess adverse events related to intranasal tolerability.

C. Clinical Abuse Potential Studies (Category 3)

In addition to their use by FDA to formulate its scheduling recommendation under the CSA for drug products containing a controlled substance, clinical studies of abuse potential, Category 3, are important for assessing the impact of potentially abuse-deterrent properties. As discussed in

[9] References suggesting that drugs associated with a rapid onset of action are associated with greater abuse potential include:

Abreu M E, Bigelow G E, Fleisher L, and Walsh S L. 2001. Effect of intravenous injection speed on responses to cocaine and hydromorphone in humans. *Psychopharmacology*, 154:76-84.

de Wit H, Bodker B, and Ambre J.1992. Rate of increase of plasma drug level influences subjective responses in humans. *Psychopharmacology*, 107:352-358.

de Wit H, Didish S, and Ambre J. 1993. Subjective and behavioral effects of diazepam depend on its rate of onset. *Psychopharmacology*, 112: 324-330.

[10] FDA has issued a draft guidance on this topic (*Assessment of Abuse Potential of Drugs).* Once finalized, it will represent FDA's current thinking on this topic.

FDA's guidance on that topic,[11] the preferred design is a randomized, double-blind, placebo-controlled and positive controlled crossover study. These studies generally are conducted in a drug-experienced, recreational user population. The use of a pre-qualification phase (see section 2 below) to identify subjects who can reproducibly distinguish active drug from placebo is a common enrichment strategy used to improve the power of the study to establish a difference between treatments.

Additional considerations applicable to clinical abuse potential studies used to assess potentially abuse-deterrent properties are discussed below. For products that are not susceptible to manipulation based on Category 1 and 2 testing, study designs for Category 3 testing should be discussed with FDA.

1. Blinding

Clinical studies of abuse potential should use a randomized, double-blind, placebo-controlled and positive controlled crossover design. Because study subjects are recreational drug users and familiar with the effects of the drug substances being studied, the double-dummy technique or other techniques should be used to ensure the blinding of all tests when possible. However, alternative designs may be suitable when the blinding of the study drug and the positive control cannot be maintained and treatment by period interactions may lead to sequence effects in a crossover design. For example, a parallel design may be useful when studying the intranasal route of administration, where subjects may be able to see the differences in volume or color between test drug and placebo or positive control, or when it is not possible to create similar results from manipulation, such as particle size from crushing. In these circumstances, early discussion with FDA is recommended.

For clinical abuse potential studies in which the subjects will snort test samples, administration of the samples in a narrow neck, opaque container with a pre-inserted straw may help facilitate blinding. However, even though subjects might not be able to see the sample, un-blinding may still occur due to the physical properties of samples with similar particle size distribution. In some formulations, higher crushed tablet/capsule volume or larger particle size may inhibit complete intranasal administration thereby contributing to the deterrence effects. To be able to evaluate these effects, it may be necessary to maintain differences in tablet/capsule volume between the potentially abuse-deterrent formulation and the comparator. To facilitate blinding and maintain the crossover design, placebos matched to each of the differing weights or particle sizes may be useful. The details of the preparation of the samples should be provided in the study protocol.

2. Pre-qualification Phase

The purpose of the pre-qualification phase is to increase the power of a study to detect differences in the abuse potential of the various formulations of drug and placebo.[12] In general,

[11] Ibid.

[12] An additional advantage of a pre-qualification phase is that it helps familiarize subjects with and train them in the use of various scales and questionnaires that measure subjective effects.

the pre-qualification phase should ensure that subjects can distinguish between placebo and a conventional IR formulation of the same opioid being developed in an abuse-deterrent formulation, using the same route of administration as planned for the assessment phase. There is little value in having subjects unable to distinguish placebo from active drug continue in the study. The positive control should include a strength that is at least equal to the lowest strength selected for the assessment during the clinical phase. An important aspect of the pre-qualification phase is assessing the ability of subjects to tolerate the study dose. If the dose used in the pre-qualification phase is lower than the lowest strength planned for the assessment phase, some subjects may not be able to tolerate the higher dose that will be administered in the assessment phase. Thus, when tolerability may be an issue, particularly if more than one dose is planned for the assessment phase, a pre-qualification dose that is no lower than the lowest dose planned may be the most efficient choice to establish that the subject can distinguish active drug from placebo and can tolerate the study drug in the range to be tested. For example, a 30 mg or 45 mg dose of opioid could be used in the pre-qualification phase when a 30 mg and 60 mg doses will be assessed in the clinical phase.

Qualifying criteria that help identify subjects with an acceptable placebo response and an acceptable response for the positive control should be pre-specified in the study protocol. After a range for an acceptable placebo response is set, a minimum value for the maximum effect (E_{max}) for the positive control should be defined. The minimum E_{max} for the positive control may vary from measure to measure, and from study to study. However, an acceptable response for the positive control should not overlap with the acceptable range for placebo response.

3. Assessment Phase

The potentially abuse-deterrent product should be compared to a positive control, and the positive control should be compared to placebo to validate the study. For an IR product with potentially abuse-deterrent properties, the positive control should be an IR formulation of the same opioid. For an ER formulation with potentially abuse-deterrent properties, the positive control could be an IR formulation of the same opioid or an ER formulation of the same opioid. In general, these studies should include one strength of the positive control which is associated with high levels of drug liking. However, when assessing drug liking through the intranasal route, the use of two strengths of the positive control may be helpful to both identify a strength of the positive control associated with high drug liking scores and to validate the study.

If there are no approved products with the same drug substance, the positive control should be a drug that, based on pharmacological profile or nonclinical data, can be expected to have similar pharmacodynamic effects. Selection of the positive control in this setting should be discussed with FDA.

4. Subjects

Studies should be conducted in opioid-experienced, recreational drug users who have experience with the particular route of abuse being studied. Subjects should generally not be physically dependent and should not be currently seeking or participating in treatment for drug abuse such that participating in the study could make them vulnerable to relapse. Depending on the

formulation being studied, however, clinical abuse potential studies can be conducted in physically dependent subjects. For example, if the deterrent product contains an opioid antagonist, clinical abuse potential studies in a physically dependent population may provide information not only on the drug liking of the product, but on the ability of the antagonist to precipitate withdrawal in this population.

Detailed characteristics of the study population with respect to past and current drug use and abuse should be captured (e.g., drugs abused, drug of choice, duration of abuse or abstinence).

5. Route of Administration, Dose Selection, Manipulation Mode, and Sample Preparation

The selection of the route(s) of administration should be based on epidemiological data showing that a selected route is a relevant route of abuse. For NMEs, the sponsor should review the relevant routes of abuse for products similar to the test product and discuss the selected routes with FDA. For each relevant route of administration, the potentially abuse-deterrent product and comparator should be manipulated based on the results of Category 1 studies to cause the highest release of the opioid and the highest plasma levels. The dose of the opioid selected for the study should be known to produce high levels of liking in non-tolerant opioid-experienced recreational users.

For studies using the intranasal route of administration, the preparation of the samples is extremely important. The potentially abuse-deterrent product and comparator study drug should be produced with similar particle size distribution based on a detailed protocol for the preparation of the samples, even if different methods are necessary to do so.[13] With some formulations, a high volume of the crushed tablet/capsule or larger particle size may inhibit complete intranasal administration and, thereby, contribute to deterrence effects. To evaluate these effects, it may be necessary to maintain differences in tablet/capsule volume between the potentially abuse-deterrent product and the comparator.

For studies using the intravenous route of administration, the oral formulations may not be safe for intravenous use depending on the excipients used in the formulation. In place of the manipulated oral formulation, a solution for injection should be prepared using approved, commercially available parenteral products when available, or products suitably formulated for the study. The amount of the opioid and that of the antagonist, when relevant, should be based on extrapolation from in vitro extraction studies of manipulated solid formulations.

6. Outcome Measures and Data Interpretation

In abuse potential studies, the primary method for evaluating the subjective effects of drugs should be through the use of standardized instruments.

[13] Available safety-related information on the use of the various excipients through the intranasal route should be provided. Additionally, some sponsors have conducted intranasal tolerability studies before the abuse potential studies to evaluate irritation of the nasal cavity, nasal congestion, and discharge, among other measures.

In typical abuse potential studies, several instruments have been used to measure subjective responses predictive of the likelihood of abuse. These instruments include:

- Visual Analogue Scales (VAS) – used for drug liking, good effects, bad effects, and other drug abuse-related effects
- Profile of Mood States

The VAS should be the primary measure for drug liking because it appears to correlate most directly with potential for abuse. Other measures of particular interest include assessment of likelihood to take the drug again and assessment of overall drug liking.[14]

These measures can be assessed using either a unipolar or bipolar scale, and a rationale should be provided for the choice for a particular scale. In general, FDA recommends using a bipolar scale for the primary measure of drug liking. Unipolar scales have been used to measure other drug effects, such as good and bad effects. Regardless of whether a unipolar or bipolar scale is selected, FDA recommends that for purposes of training subjects, the same scale be used in the pre-qualification and assessment phases.

7. Data Interpretation

For clinical studies of abuse potential conducted on potentially abuse-deterrent opioid drug products, the primary analysis should be the difference in means of the E_{max}[15] for the primary measure(s) based on the population of study completers. A statistical analysis plan (SAP) should be included in the study protocol or submitted as a separate document before un-blinding the study. The sponsor should provide data and dropout information for non-completers. To ensure adequate power, the sponsor should take into account that there will be subjects who drop out of the study early and plan the sample size calculation accordingly. Proper planning should avoid any need to replace subjects who discontinue without completing the study.

Additional pharmacodynamic measures, including positive subjective effects other than drug liking (e.g., take drug again, high, overall drug liking) and other subject-rated assessments, are generally considered secondary endpoints. Other subject-rated assessments of interest include: alertness; drowsiness; nausea; and, when the intranasal route is used, intranasal irritation, burning, need to blow nose, runny nose/nasal discharge, facial pain/pressure, and nasal congestion.

Some sponsors provide descriptive statistics including mean, standard error, median, and interquartile range, calculated for all pharmacodynamic endpoints by time and treatment.[16] What

[14] *Overall drug liking* measures the user's retrospective assessment of a drug, whereas *VAS for drug liking* measures the user's immediate assessment.

[15] In general, the primary endpoint of interest is drug liking, and the E_{max} is captured within 8 hours after dosing. However, the timeframe of measuring the maximum response will be determined by the pharmacokinetic and pharmacodynamic parameters of the formulations studied.

[16] See *Statistical Analysis* Section for further guidance.

constitutes a clinically significant difference in drug liking, between the manipulated and intact versions of the potentially abuse-deterrent product and positive control, is an area requiring further research and will be evaluated on a case-by-case basis. Analysis of postmarket data on abuse levels associated with the potentially abuse-deterrent product being studied may help to support the findings from abuse potential studies.

In addition, when interpreting results from clinical abuse potential studies, attention should be given to the profile of subjective effects produced by the manipulated and intact formulation in terms of onset, peak duration of activity, and offset. The rate of rise of drug onset for the intact and manipulated potentially abuse-deterrent product should be given appropriate weight in the overall analysis of the abuse-deterrent properties. A more rapid onset of action or a shorter time-to-reach peak effect is generally associated with greater abuse potential. Regarding the duration of effect, it may be difficult to interpret the abuse potential of a formulation that produces a sustained liking effect when taken intact or after manipulation, though lower than that produced by the positive control formulation.

The overall assessment of abuse potential should be based on the pattern of findings across all of the measures. In addition, qualitative aspects of the findings, such as the steepness of the drug liking response and duration of the liking effects associated with manipulated formulations, should be taken into consideration, along with other positive effects and negative effects.

8. Statistical Analysis

a. Background

The overall goal of a clinical study of abuse potential is to assess a number of abuse potential outcome measures (e.g., drug liking VAS) in the potentially abuse-deterrent product (*T*) relative to a formulation of the drug without abuse-deterrent properties (*C*), or a newly formulated opioid product (positive control). Substantial decreases in the responses for the potentially abuse-deterrent formulation compared to the positive control are evidence of deterrence.

A clinical study of abuse potential should be validated by comparing the responses to *C* with those of placebo (*P*). Thereafter, the assessment of the abuse-deterrence properties of *T* is of primary interest. This can be achieved by comparing the difference in means between *C* and *T* with a *margin* for abuse potential measures and comparing the difference between *C* and *T* relative to *C* in drug liking on a bipolar VAS.

The statistical analysis of the data in a clinical study should begin with descriptive statistics making up tabulations and graphs that include tables of the mean, standard error, and other summary statistics: minimum, Q1, median, Q3, and maximum of the responses of interest for each treatment and for each paired difference among treatments.

Useful graphs include mean time course profiles, heat-maps,[17] and continuous responder profiles.

The next subsection describes the statistical test that sponsors should use for the primary analysis of E_{max} on the VAS for drug liking. An analysis of the percent reduction in drug liking for *T* relative to *C* on the individual level in subsection c is recommended as a secondary analysis.

b. Primary analyses

The primary analysis of abuse-deterrent effects should be based on the comparison of means[18] between crushed, chewed, or otherwise modified *T* and *C* with an abuse deterrence margin on drug liking VAS. That is, test

$$H_0 : \mu_C - \mu_T \le \delta_1 \text{ versus } H_a : \mu_C - \mu_T > \delta_1$$

where $\delta_1 = \delta^*(\mu_C - 50)$, and $0 < \delta^* < 1$. Because *C* is an opioid drug, the validation test also needs a margin, say δ_2. That is,

$$H_0 : \mu_C - \mu_P \le \delta_2 \text{ versus } H_a : \mu_C - \mu_P > \delta_2$$

where $\delta_2 \ge 15$.

The significant level for both tests is 2.5%.

The actual value of δ_1 is related to μ_C, hence, it may vary according to abuse potential measures and the route of drug administration. The δ^* should be pre-specified in the protocol. We also suggest the use of 95% confidence intervals to assess both the differences $\mu_C - \mu_T$ and $\mu_C - \mu_P$.

c. Secondary analyses

In addition to the primary analysis, an analysis should be performed of the percent reduction for the potentially abuse-deterrent product *T* relative to *C* from each individual study subject for drug liking VAS on a bipolar scale from 0 to 100. One definition for percent reduction for individual subjects is as follows:

$$\%reduction = \frac{c_i - t_i}{c_i - p_i} \times 100\%,\ i = 1, 2, ..., n,$$

where c_i, t_i and p_i are the E_{max} values for *C*, *T*, and *P* from the *i*th subject, respectively; n is the sample size.

[17] Chen L and Wang Y. 2012. Heat map displays for data from human abuse potential crossover studies. *Drug Information Journal*, 46:701:707.

[18] If a nonparametric method is necessary, analysis of the median difference in E_{max} may be appropriate.

However, this definition is problematic because for two subjects having the same E_{max} values for T and C ($t_1 = t_2$ and $c_1 = c_2$), the larger the placebo response, the greater the percent reduction. A more appropriate definition of percent reduction can be derived by replacing p_i by the neutral score 50 on a bipolar scale; that is,

$$\% \text{ reduction} = \frac{c_i - t_i}{c_i - 50} \times 100\%,\ i = 1, 2, ..., n$$

where we assume that $c_i > 50$. In case some subjects have $c_i \leq 50$, define % reduction = 0.

Note that even though most abuse potential studies have a pre-qualification phase, approximately 10% of subjects still have placebo responses p_i over 65, with 5% over 75 in the assessment phase. Consequently, it may be necessary to penalize subjects with large values of p_i in computing percent reduction. For example, the percent reduction could be multiplied by an adjustment factor that equals 1 when p_i is around 50 or less and decreases from 1 when p_i is large. Sponsors should discuss with FDA the need for an adjustment factor in computing percent reduction and an appropriate formula for defining the penalty to be applied before finalizing the study protocol.

Two approaches for assessing the deterrent effects using percent reduction for crossover design studies are provided below. Note that when a parallel design is used, the percent reduction for individual subjects is not applicable, and the primary analysis may also serve the purpose for assessing the percent reduction based on $\mu_C - \mu_T$ related to $\mu_C - 50$.

- Responder Analysis

A *responder* is defined as a subject who had at least $\delta^*100\%$ of reduction, in E_{max} for *T* relative to *C*. To ensure that a majority of subjects are responders, a proportion test can be used to test the null hypothesis that 50% or fewer subjects are responders. That is, test

$H_0 : p^* \leq 50\%$ versus $H_a : p^* > 50\%$

at the 2.5% significance level where *p** denotes the percentage of responders. The 95% confidence interval of *p** can also be calculated.

- Analysis of the Median Percent Reduction

The median of the percent reduction (*ptr*) is a descriptive measure of central tendency of *ptr*. At most 50% of subjects have *ptr* less than the median, and at most 50% of subjects have *ptr* greater than the median. If the median of *ptr* is equal to 30%, for example, it means that approximately 50% of subjects have greater than or equal to a 30% reduction.

For assessing deterrent effects, we can test

$$H_0 : median(ptr) \leq DR\% \text{ versus } H_a : median(ptr) > DR\%$$

at the 2.5% significance level, where DR denotes deterrent reduction. To be consistent with the responder analysis, we recommend DR % = $\delta^*100\%$. If the distribution of *ptr* is symmetric, the Wilcoxon-signed rank test can be used to test the null hypothesis that the $median(ptr) \leq DR\%$, and a 95% confidence interval for the median based on this test can be readily calculated using standard methods. Otherwise, the sign test should be used or an alternate method of this test can be pre-specified in the SAP.

Sponsors should pre-specify one of the two analysis methods for the percent reduction in their SAP in addition to the primary analysis in their clinical studies and discuss with FDA the definition of a responder in the responder analysis or the value of DR% used in the analysis of the median percent reduction before finalizing the study protocol.

d. Multiplicity

Whether or not an adjustment for multiplicity is needed for claiming significant results on the primary or key secondary endpoints varies from study to study. Sponsors should refer to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidance *E9 Statistical Principles for Clinical Trials*[19] for statistical principles regarding the multiplicity adjustment.

V. POSTMARKET STUDIES (CATEGORY 4)

Premarket studies focus on assessing the potentially abuse-deterrent properties of a product under controlled conditions. The goal of postmarket[20] studies, Category 4, is to determine whether the marketing of a product with abuse-deterrent properties results in meaningful reductions in abuse, misuse, and related adverse clinical outcomes, including addiction, overdose, and death in the post-approval setting. As more abuse-deterrent products are approved, it is possible that the amount of reduction observed in an epidemiologic study may also change. Consequently, a reduction that is deemed meaningful at one time may not be meaningful at another. Given the changing landscape, a numerical threshold cannot define what would be considered a meaningful reduction.

Currently, data on the impact of an abuse-deterrent product on drug abuse in the U.S. population are limited, and thus the optimal data sources, study variables, design features, analytical

[19] ICH guidelines are available on FDA's guidance webpage at http://www.fda.gov/RegulatoryInformation/Guidances/default htm.

[20] FDA requires postmarket studies for all opioids with abuse-deterrent labeling claims. For more information on postmarket requirements, see http://www fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/ucm070766.htm.

techniques, and outcomes of interest of postmarket epidemiologic studies are not fully established.

Postmarket evaluations of abuse deterrence fall into two categories—formal studies and supportive information. Sponsors should submit protocols to FDA for all formal studies of abuse deterrence. Supportive information can also be submitted to FDA, but cannot substitute for formal studies.

A wide range of interrelated behavioral, clinical, and societal factors contribute to drug abuse; therefore, the effects of an abuse-deterrent formulation can manifest in a variety of ways. Understanding the actual impact of a particular abuse-deterrent formulation may require using a variety of study designs to examine different abuse-related outcomes in given populations of interest. Generally, multiple formal studies using a variety of data sources should be conducted to provide insights into product-specific abuse and the effect of an abuse-deterrent product on the outcomes of interest for other opioid drug products. The use of multiple study designs will also generally help with assessment of the impact of abuse-deterrent products on the full spectrum of abuse-related outcomes (i.e., addiction, overdose, and death) and to characterize and quantify the relevant clinical events that are associated with these outcomes.

Recognizing that the current thinking in this area may change, the following subsections provide recommendations for designing postmarket epidemiologic studies that are capable of detecting a change in the occurrence of abuse as a result of a drug product's abuse-deterrent properties.

A. Formal Studies

1. General Characteristics

Formal studies have the following characteristics:

1. They are hypothesis-driven, population-based, observational evaluations that follow good epidemiological practices[21,22] and use outcomes that provide meaningful measures of abuse deterrence.
2. They capture one or more outcomes that can be used to assess meaningful reductions in misuse, abuse, addiction, overdose, and death.
3. They produce estimates of abuse and related clinical outcomes that are nationally representative, or are based on data from multiple large geographic regions that can reasonably be generalized to the national level. In the absence of nationally generalizable

[21] See FDA guidance *Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data*, available at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm243537.pdf.

[22] International Society for Pharmacoepidemiology and Risk Management, Guidelines for Good Practices and Pharmacoepidemiologic Studies, available at http://www.pharmacoepi.org/resources/guidelines_08027.cfm, accessed January 25, 2015.

data, smaller or regional studies may be informative, but must be accompanied by a clear explanation of their representativeness and generalizability for appropriate interpretation.

4. They assess overall and route-specific (i.e., injected, snorted, smoked) changes in abuse levels that are associated with an abuse-deterrent product.
5. They are sufficiently powered statistically to assess meaningful changes in drug abuse and are of sufficient duration to examine trends in abuse following the marketing of the abuse-deterrent product. The necessary duration of the studies will depend on a variety of factors, including drug utilization and market share, early postmarket abuse deterrence data, and changes in the prescription opioid or illicit drug market.

2. Study Design Features

The epidemiologic methods and data sources that underlie formal postmarket studies to evaluate the effect of abuse-deterrent formulations are evolving, and best practices have not been established. In addition, characterizing the relevant clinical events that are most useful for understanding the actual impact of a product on abuse-related adverse events is also an evolving science. Based on the current state of this field, we provide below some basic guidelines on recommended study design features that will enable FDA to evaluate the results of formal studies.

1. The study hypothesis and its relationship to assessing abuse deterrence should be clearly stated. The study hypothesis should also include the route(s) of abuse that will be studied.
2. An understanding of each data source is important to the design and interpretation of the study. A description of each data source should be provided in the protocol and should include if and how the data source captures drugs, study outcomes, drug formulation, and route of abuse. The sampling methods, study population, or catchment area for the data source should be clearly described.[23]
3. The choice of population(s) in each study should be carefully considered. The populations included in the study should be described in the protocol. At least one study should include a high-risk population, such as a population of known drug abusers, but formal studies should not be limited to only high-risk populations.
4. The protocol and study reports should thoroughly define the study outcomes. The choice of the outcome measure(s) should be justified. Formal studies should, as a group, capture all relevant outcomes: misuse, abuse, addiction, overdose, and death, as well as misuse and abuse clinical outcomes. Overall and route-specific misuse and abuse estimates should include prevalence and frequency of abuse. Clinical outcomes should include, when possible, an assessment of severity of abuse outcomes (e.g., addiction or overdose).

[23] See FDA guidance *Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data.*

5. Both population- and drug utilization-based estimates should be included in the study protocol.[24] Drug utilization-based estimates should use multiple denominators. The denominators are generally the number of prescriptions and the number of extended units (e.g., tablets or capsules). The catchment area for drug utilization data should be specified, particularly for sub-national or regional populations.
6. Sponsors should list all proposed opioid comparators and describe the rationale behind their inclusion. When branded and generic versions of a comparator are marketed, all should be included in the study when possible because many data sources used in abuse studies can identify only active ingredients and do not distinguish between branded and generic products or among multiple generic products. Information should be provided on the ability of data sources and study participants to accurately discriminate among different opioid products and formulations. The choice of comparator is critical for determining if a reduction in drug abuse is the result of a product's abuse-deterrent properties or the result of other factors (e.g., educational programs, prescription drug monitoring programs, changes in law enforcement policies, and the availability of other drugs) or secular trends. The choice of comparators will depend on the particular abuse-deterrent product studied and the opioid market environment at the time the study is initiated. Multiple comparators should be used to achieve the most complete picture of the impact of a product's abuse-deterrent properties. For the purposes of hypotheses, some comparators should be selected and justified as primary comparators in the study protocol before data collection, with additional comparators providing context. The following are examples of several potential abuse-deterrent study comparator scenarios.

    If an abuse-deterrent formulation of a previously marketed product is introduced to the market, the primary comparators should include historical and currently available non-abuse-deterrent formulations of the products (including branded and generic whenever possible). Additional individual opioid products should be included as well and should be agreed upon with FDA and identified before the start of the study.

    If a new abuse-deterrent product does not have an historical or currently available non-abuse-deterrent version of the same opioid, an appropriate group of comparators should be identified before the start of the study through mutual agreement with FDA. Examples of appropriate primary comparators include immediate release non-abuse-deterrent products with the same active moiety and/or a non-abuse-deterrent product with a relatively stable market share and abuse estimates captured at baseline during the postmarket period. Larger groupings of products can also serve as comparators and can help determine secular trends.

    When available, a product that has the same active moiety, but has a different abuse-deterrent property, can serve as a comparator.

[24] Secora A, Dormitzer C, Staffa J, and Dal Pan G. 2014. Measures to quantify the abuse of prescription opioids: a review of data sources and metrics. *Pharmacoepidemiology and Drug Safety*, 23(12):1227-37.

7. Understanding the background rates of drug abuse is important for protocol design and interpretation of study results. A baseline assessment of the prevalence of drug abuse for formulations of the same opioid that lack abuse-deterrent properties should be conducted and the baseline time period should be justified.
8. Submissions should include the SAP. The plan should include parameter definitions, unit of analysis, model specification, power and sample size calculations, and any additional variables or predictors. Assessment of the abuse outcome measures should consider both average levels of abuse comparing pre- and post-periods to currently available product (means analysis) and trend analysis.
9. Statistical models should include variables that may affect how the product is used and also other related confounders (e.g., geographic variability and demographic characteristics).
10. Exposure and outcome measures that include self-reported assessments should be validated before the start of the study.
11. The precision of outcome measures will also influence the observational period. Outcome measures with large uncertainty (due to bias or variability) in the exposure or study variable measures, for example, may warrant longer observational periods.
12. Interim analyses are encouraged, but results should be considered tentative in light of their preliminary nature.

B. Supportive Information

Information is considered supportive if it can be used to provide additional context on societal, behavioral, and clinical aspects of abuse and abuse-deterrence. Supportive information may be qualitative or descriptive, and it may rely on sources that capture drug utilization or prescribing patterns, diversion events, attitudes and practices (e.g., tampering) of abusers and other information that may not directly be considered abuse (e.g., data concerning the street value of prescription drugs, information about drug use and misuse from social websites). Investigations that provide supportive information may also include investigations that are conducted in smaller populations or subgroups, and that while perhaps not broadly generalizable, may contribute to the totality of the evidence relating to abuse deterrence.

As is the case for formal studies, best practices for collecting and submitting supportive information are still evolving. However, below are some basic recommendations relating to supportive information.

1. Supportive information should be clearly stated, and the rationale for how the supportive information contributes to a sponsor's portfolio of abuse-related studies should be clearly identified.
2. How supportive information is representative of the population from which it is derived or sampled should be clearly described.

3. How the exposure and outcome are measured should be clearly described along with the relationship between the outcomes measured and the primary outcomes of interest: misuse, abuse, addiction, overdose, and death.
4. Collections of supportive information that include populations of particular interest or geographically diverse settings is strongly encouraged. Overlapping geographic areas between formal and supportive information should be considered.

VI. LABELING

Including information about a product's abuse-deterrent properties in labeling is important to inform health care professionals, the patient community, and the public about a product's abuse potential. Accordingly, FDA encourages sponsors to propose labeling that sets forth the results of in vitro, pharmacokinetic, clinical abuse potential and formal postmarket studies and appropriately characterizes the abuse-deterrent properties of a product.

There are several important concepts about the state of the science of pre- and postmarket studies of abuse deterrence that should be considered as these are reflected in labeling. First, as stated earlier in the guidance, abuse-deterrent does not mean abuse-proof. Therefore, labeling should reflect a product's abuse-deterrent properties, as supported by the data, but should include a caveat that abuse is still possible. Next, premarket studies are intended to demonstrate properties that are predictive of a meaningful abuse-deterrent effect for a particular route of administration. FDA has limited data correlating the abuse-deterrent properties of certain opioid drug products, as demonstrated by premarket studies, with the impact of those properties on abuse or adverse events associated with abuse in the post-approval setting. Even though postmarket studies have the potential to demonstrate such effects, the findings of postmarket studies are not available at the time of initial product approval. Labeling should reflect the predictive quality of premarket studies and include results of relevant completed postmarket studies.

When premarket data show that a product's abuse-deterrent properties can be expected to result in a meaningful reduction in that product's abuse, these data, together with an accurate characterization of what the data mean, should be included in product labeling.[25] When postmarket data become available that demonstrate a meaningful reduction in abuse by one or more routes of administration, these data should be added to the product labeling. However, if these postmarket data fail to confirm that the abuse-deterrent properties result in a reduction in abuse, or demonstrate a shift in routes of abuse that represent a greater risk (e.g., a shift from oral and nasal abuse to intravenous abuse), FDA may determine that labeling revisions are needed.

Labeling language regarding abuse deterrence should describe the product's specific abuse-deterrent properties as well as the specific routes of abuse that the product has been developed to deter. For example, a formulation that limits an abuser's ability to crush a tablet and to extract the opioid can be described as limiting manipulation for the purpose of snorting or injection if

[25] Abuse-deterrence information in labeling should be presented in the DRUG ABUSE AND DEPENDENCE section under 9.2 Abuse.

the data support such a statement. For this characterization to be accurate and not misleading, however, appropriate caveats are likely to be necessary as described above. For example, a product's labeling should explain that the product's abuse-deterrent properties only make abuse more difficult, not impossible, and that these properties provide no deterrence against other potential forms of abuse.

As noted at the outset of this guidance, FDA will take a flexible, adaptive approach to the evaluation and labeling of abuse-deterrent opioid products. FDA expects sponsors to update their formulations to take advantage of technological improvements and further expects to allow labeling statements related to abuse deterrence commensurate with those advances.

Furthermore, FDA expects sponsors to compare their formulations against approved abuse-deterrent versions of the same opioid. The comparisons should be based on the relevant categories of testing. For instance, if a proposed product is less resistant to manipulation than an approved product, the proposed product may not be eligible for labeling regarding abuse-deterrent properties.

FDA is concerned that, with time, abusers may adapt to abuse-deterrent technologies and discover methods to defeat them. If and when abusers can overcome a technology such that it no longer has a meaningful effect in deterring abuse, FDA may require labeling revisions.

As discussed below, the nature of information in labeling on abuse deterrence for a particular product will depend on the types of studies performed and the result of those studies. Because it cannot provide specific guidance on the magnitude of effect that would be sufficient to support each type of claim, FDA will assess the appropriateness of all proposed labeling statements about abuse deterrence based on the data provided.

Information describing the results of the evaluation of abuse-deterrent properties can be used to support labeling statements based on the three premarket categories (i.e., in vitro data, pharmacokinetic data, and clinical abuse potential studies) and the fourth category (postmarket data) once it is available.

The data necessary to support abuse-deterrent labeling will depend on the characteristics of the product that impart the abuse deterrence and the route of abuse. In general, most abuse-deterrent information included in product labeling will be based on data from more than one category.

Key elements of the study design and conduct should be summarized in the product labeling. Category 1 studies can be described in general terms to avoid creating a *road map* for defeating the product's abuse-deterrent properties. However, the design, conduct, and results of Category 2 and 3 studies should be described in sufficient detail, including the primary outcome measure data from Category 3 studies, to support clear labeling regarding a product's abuse-deterrent properties.

The following are examples of information for inclusion in labeling for different types of abuse-deterrent effects based on various types of premarket studies performed.

- Category 1

For this product, in vitro data demonstrated that an abuse-deterrent product cannot be crushed and dissolved or extracted in a small volume of solution suitable for injection. In this case, Category 1 in vitro data may be sufficient to support a statement in labeling about abuse deterrence for the intravenous route of abuse (See Section IV Premarket Studies). Possible labeling text:

> *In vitro physical and chemical tablet manipulation studies were performed to evaluate the ability of different extraction methods to defeat the formulation. Results support that Tradename resists crushing, breaking, and dissolution using a variety of tools and solvents and retains some extended-release properties despite manipulation.*
>
> *These in vitro data demonstrate that Tradename has physical and chemical properties that are expected to deter intravenous abuse. However, abuse of this product is still possible by the oral and nasal routes.*

- Category 1 and Category 2

For this product, in vitro and pharmacokinetic data from study of the oral and nasal routes of administration demonstrated that no changes occurred in the extended-release properties of the opioid after crushing or dissolution in a variety of solvents. These data may be sufficient to support statements in labeling about abuse deterrence for the nasal and intravenous routes of abuse. Possible labeling text:

> *In vitro physical and chemical tablet manipulation studies were performed to evaluate the ability of different extraction methods to defeat the formulation, and pharmacokinetic studies of the oral and intranasal routes were performed to determine the effect of manipulation on drug release. Results support that Tradename resists crushing, breaking, and dissolution using a variety of tools and solvents and retains its extended-release properties despite manipulation.*
>
> *The in vitro data demonstrate that Tradename has physical and chemical properties that are expected to deter oral, nasal and intravenous abuse. However, abuse of intact product is still possible by the oral route.*

- Category 2 and Category 3

For this product, pharmacokinetic and clinical abuse potential studies demonstrated the release of an antagonist from an opioid and antagonist combination product following crushing and that the presence of the antagonist resulted in less drug liking compared to a similar amount of opioid alone when administered by the oral and intranasal routes. In

addition, an additional clinical abuse potential study simulating intravenous abuse using the amounts of opioid and antagonist found to be released from the crushed product also demonstrated reduced drug liking.

> *The pharmacokinetic data demonstrate that crushing Tradename results in the simultaneous release and rapid absorption of opioid and antagonist. These data along with the results from oral and intranasal clinical abuse potential studies and a clinical abuse potential study of intravenous opioid and antagonist to simulate crushed Tradename indicate that Tradename has properties that are expected to deter abuse via the oral, intranasal, and intravenous routes. However, abuse of Tradename by these routes is still possible.*

All of these statements based on Categories 1, 2, or 3 testing should be followed by a statement that data from laboratory and clinical studies may not fully predict abuse potential in the post-approval setting.

As discussed in Section V, postmarket data from a variety of sources can demonstrate that a product's abuse-deterrent properties result in persistent and relevant abuse deterrence. These data can result from appropriately designed, conducted, and analyzed formal postmarket studies and from supportive information on the abuse of the product.

FDA is currently considering formal studies plus a variety of supportive information (e.g., data concerning the street value of prescription drugs) as sources that may be acceptable to provide evidence that a product's formulation has had an actual impact on reducing its abuse. FDA anticipates that data from some or all three of the premarket categories along with data from postmarket studies (including both formal studies and supportive information) would be needed to support a statement in labeling that the product has been shown to reduce abuse. The combined results from all of these studies would be described in the product labeling, including specific study designs, conduct, analyses, and study data.

An example of labeling for a product with evidence of a reduction in abuse is:

> *These data demonstrated a reduction in the abuse of Tradename in the community setting compared to the levels of abuse, overdose, and death that occurred when only formulations of the same opioid without abuse-deterrent properties were available. This reduction in abuse appears to be attributable to the product's formulation, which deters abuse by injection or snorting of the manipulated product. However, such abuse of this product is still possible, and the product's abuse deterrence properties do not deter abuse associated with swallowing the intact formulation.*

VII. ADDITIONAL RESEARCH NEEDS

As discussed above, the science of abuse deterrence is relatively new. Both the technologies involved and the analytical, clinical, and statistical methods for evaluating those technologies are

rapidly evolving. For these reasons, FDA will take a flexible, adaptive approach to the evaluation and labeling of potentially abuse-deterrent opioid products. Additionally, there is considerable room for additional scientific work that could advance the development and assessment of abuse-deterrent products. In particular, FDA encourages additional research on the following topics:

- The quantitative link between changes in the pharmacokinetics of opioids in different formulations and results of a clinical abuse potential study with those same formulations.
- The best assessment methods to employ when analyzing a clinical study of abuse potential.
- The quantitative link between the outcomes from a clinical study of abuse potential comparing formulations and the effect on those same formulations on abuse in the community.
- Further understanding of the best study methods to employ to assess the effect of a product with abuse-deterrent properties on the rates of abuse in the community.
- Development of a communication tool (e.g., a simple graph or chart) to inform prescribers of the relative impact the product has on the different routes of abuse.

Progress on these topics could facilitate the ability of sponsors to propose and FDA to approve labeling that would give a more complete picture of the anticipated effect of products with abuse-deterrent properties. Ultimately, progress in these areas could facilitate product development by reducing the amount of information that is needed to accurately assess a product with abuse-deterrent properties and predict its impact on abuse in the community.

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Drug Utilization Review

Date:	August 6, 2015
Reviewer:	Rajdeep Gill, Pharm.D. Drug Use Data Analyst, Team Leader Division of Epidemiology II
Deputy Director For Drug Utilization:	LCDR Grace Chai, Pharm.D. Division of Epidemiology II
Director:	Judy Staffa, RPh., PhD. Division of Epidemiology II
Subject:	Drug utilization patterns of oxycodone extended-release (ER) and oxycodone single-entity immediate-release (SE IR)
Drug Name(s):	Oxycodone extended-release (ER), Oxycodone single-entity immediate-release (SE IR)
Application Type/Number:	multiple
Applicant/sponsor:	multiple
OSE RCM #:	2015-1432

This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information in this document has been cleared for public release.

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EXECUTIVE SUMMARY

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested Division of Epidemiology II (DEPI II) to provide drug utilization patterns for oxycodone extended-release (ER) and oxycodone single entity (SE) immediate-release (IR), stratified by products from 2010 through 2014. The drug utilization data will assist DAAAP in preparation for the upcoming joint meeting of the Drug Safety and Risk Management Advisory Committee (DSARM) and the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC), scheduled on September 10, 2015 to discuss new abuse deterrent formulations of oxycodone. Because the majority of oxycodone ER and oxycodone SE IR were sold to U.S. outpatient retail pharmacies, this review is focused on outpatient retail pharmacy settings.

In 2014, approximately 4.7 million oxycodone ER prescriptions were dispensed and 975,000 unique patients received dispensed prescriptions for oxycodone ER. Reformulated OxyContin accounted for approximately more than 99% of the total prescriptions dispensed and total patients receiving oxycodone ER prescriptions dispensed in 2014.

Approximately 15.8 million oxycodone SE IR prescriptions were dispensed and 5 million patients received dispensed prescriptions for oxycodone SE IR in 2014. Approximately 300 Oxecta prescriptions were dispensed and approximately 200 patients received a dispensed prescription for Oxecta in 2014.

1 INTRODUCTION

In preparation for the joint meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee, scheduled on September 10, 2015, this review summarizes outpatient retail drug utilization patterns of oxycodone ER and oxycodone SE IR, stratified by products, with a focus on recently reformulated oxycodone formulations from 2010 through 2014.

1.1 PRODUCT INFORMATION

OxyContin (oxycodone hydrochloride, controlled-release) was approved (NDA 020553) by FDA on December 12, 1995 "for the management of moderate to severe pain where use of an opioid analgesic is appropriate for more than a few days." Reformulated OxyContin (oxycodone hydrochloride, extended-release) was approved (NDA 0220271) on April 5, 2010 for the "management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate." Marketing of the reformulated OxyContin began in August 2010**.** As of August 10, 2010, the sponsor ceased shipment of original OxyContin.[1]

Oxycodone SE IR was originally approved in 1982 and Oxecta (immediate-release oral formulation of oxycodone HCl) was approved (NDA 202080) on June 17, 2011. Oxecta is indicated for the management of acute and chronic moderate to severe pain where the use of an opioid analgesic is appropriate.[2]

2 METHODS AND MATERIAL

[1] http://www.accessdata fda.gov/drugsatfda_docs/label/2014/022272s022lbl.pdf, accessed May, 2015

[2] http://www.accessdata fda.gov/drugsatfda_docs/nda/2011/202080Orig1s000LBL.pdf, accessed July, 2015

2.1 DETERMINING SETTINGS OF CARE

IMS Health, IMS National Sales Perspectives™ (see Appendix 2 for full description) was used to determine various retail and non-retail channels of distribution for single entity oxycodone products. Sales data for year 2014 indicated that approximately 75% of oxycodone ER and 69% of oxycodone SE IR bottles were distributed to outpatient retail pharmacies (including chain, independent, and food stores).[3,4] As a result, outpatient retail pharmacy utilization patterns were examined in this review. Mail-order/specialty, hospital, and other non-retail pharmacy settings data were not included in this analysis.

2.2 DATA SOURCES USED

Proprietary drug utilization databases available to the Agency were used to conduct this analysis (see Appendix 2 for full database description).

IMS Health, National Prescription Audit (NPA) was used to obtain the nationally estimated number of prescriptions dispensed for oxycodone ER and oral solid oxycodone SE IR, from outpatient retail pharmacies, 2010 through 2014. Only oral solid oxycodone SE IR formulations were included in these analyses because liquid oxycodone products accounted for <1% of total oral oxycodone prescriptions in 2014.[5]

IMS Health, Total Patient Tracker (TPT) was used to obtain the nationally estimated number of unique patients, receiving oxycodone ER and oral solid oxycodone SE IR prescriptions dispensed from U.S. outpatient retail pharmacies, 2010 through 2014.

3 RESULTS

3.1 PRESCRIPTION DATA FOR OXYCODONE ER AND OXYCODONE SE IR

Table 1 in Appendix 1 shows the nationally estimated number of oxycodone ER and oxycodone SE IR prescriptions, stratified by products, dispensed from U.S. outpatient retail pharmacies from 2010 through 2014.

The total number of oxycodone SE IR prescriptions increased from 10.4 million prescriptions dispensed in 2010 to 15.8 million prescriptions dispensed in 2014, accounting for 52% increase. An estimated 295 prescriptions (less than 0.1% of total oxycodone SE IR) of Oxecta were dispensed in 2014 and all other oxycodone SE IR accounted for nearly 100% of the total prescriptions dispensed.

The total number of oxycodone ER prescriptions decreased from approximately 7.3 million prescriptions dispensed in 2010 to 4.7 million prescriptions dispensed in 2014 accounting for 35% decrease. Reformulated OxyContin accounted for approximately 21% (1.5 million prescriptions) of the total oxycodone ER prescriptions dispensed in 2010 and accounted for 99.6% of total oxycodone ER prescriptions dispensed in 2014.

3.2 OXYCODONE ER AND OXYCODONE SE IR UNIQUE PATIENT DATA

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[3] IMS Health, National Sales Perspectives™, Data extracted 05/2015, File: NSP 2015-309 Oxy ER sales dis 05-11-15.xlsx

[4] IMS Health, National Sales Perspectives™, Data extracted 07/2015, File: NSP Oxy IR channels 07-14-15.xlsx

[5] MS Health, National Prescription Audit (NPA™) Data extracted 06/2015, File: NPA 2015-309 oxycodone by form.xlsx

Table 2 in Appendix 1 shows the nationally estimated number of unique patients receiving dispensed prescriptions for oxycodone ER and/or oxycodone SE IR from the U.S. outpatient retail pharmacies from 2010 through 2014.

The total number of unique patients receiving oxycodone IR prescriptions increased from approximately 3.3 million patients in 2010 to 5 million patients in 2014, approximately 52% increase. An estimated 206 unique patients (less than 0.1% of total patients receiving oxycodone SE IR) received a dispensed prescription for Oxecta in 2014. Nearly 100% of the patients received a dispensed prescription for generic oxycodone SE IR in year 2014.

The total number of unique patients receiving oxycodone ER prescriptions decreased from approximately 1.5 million patients in 2010 to 975,000 patients in 2014, approximately 34% decrease. Patients that received reformulated OxyContin prescriptions accounted for 99.6% of the total patients for oxycodone ER products in 2014.

4 DISCUSSION

The findings from this review illustrate that utilization of oxycodone ER decreased by approximately 35% during the 5-year time period from 2010 through 2014. In 2014, reformulated OxyContin accounted for nearly all utilization of extended-release formulations; however, it appears residual prescriptions and patients utilization for oxycodone ER (generics or original OxyContin formulation) products continue to be dispensed. Of note, the reformulated OxyContin (oxycodone ER) was reformulated with abuse deterrent properties intended to discourage misuse and abuse by preventing the opioid medication from being cut, broken, chewed, crushed or dissolved to release more medication.[6] Oxycodone SE IR utilization increased by 50% during the study period. Although Oxecta was approved in July 2011, minimal use was observed for Oxecta during the study period.

Findings from this review should be interpreted in the context of the known limitations of the databases used. Based on the IMS Health, IMS National Sales Perspectives™, sales data for year 2014 showed that majority of oxycodone ER and IR bottles were distributed to outpatient retail pharmacies. We focused our analysis on only the outpatient retail pharmacy settings; therefore, these estimates may not apply to other settings of care in which these products are used (e.g. mail-order setting, clinics, non-federal hospitals, etc.). The estimates provided are national estimates, but no statistical tests were performed to determine statistically significant changes over time or between products.

5 CONCLUSIONS

U.S. outpatient retail pharmacy utilization patterns analyzed in this review suggest that utilization of oxycodone SE IR increased by approximately 50% during 5-year time period studied from 2010 through 2014. Oxecta accounted for less than 0.1% of oxycodone SE IR utilization during the study period. Utilization of oxycodone ER decreased by approximately 35% from 2010 through 2014. After reformulation of Oxycontin (oxycodone ER) in 2010, utilization of reformulated OxyContin increased and accounted for nearly 100% of total utilization in 2014. Although very low, residual utilization of generic oxycodone ER and/or original OxyContin was observed during the study period from 2010 through 2014.

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[6] http://www fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm207480 htm

APPENDIX 1: TABLES

Table 1. Nationally Estimated Number of Dispensed Prescriptions for Oxycodone Extended Release (ER) and Oral Solid Formulations of Oxycodone Single-Entity (SE) Immediate-Release (IR), Stratified by Products, from U.S. Outpatient Retail Pharmacies, Years 2010-2014

	2010		2011		2012		2013		2014	
	TRx	*Share*	TRx	*Share*	TRx	*Share*	TRx	*Share*	TRx	*Share*
	N	*%*	N	*%*	N	*%*	N	*%*	N	*%*
Total Oxycodone SE IR and ER	17,714,678	*100%*	19,128,928	*100%*	19,125,875	*100%*	19,242,817	*100%*	20,512,710	*100%*
Single-Entity Immediate-Release Formulations	10,433,669	*58.9%*	13,297,405	*69.5%*	13,977,244	*73.1%*	14,377,328	*74.7%*	15,813,556	*77.1%*
Oxycodone SE IR	10,433,669	*100%*	13,297,405	*100%*	13,976,982	*100%*	14,376,780	*100%*	15,813,261	*100%*
Oxecta					262	*0.0%*	548	*0.0%*	295	*0.0%*
Extended-Release Formulations	7,281,009	*41.1%*	5,831,523	*30.5%*	5,148,631	*26.9%*	4,865,489	*25.3%*	4,699,154	*22.9%*
Reformulated OxyContin	1,541,563	*21.2%*	5,537,806	*95.0%*	5,112,356	*99.3%*	4,850,153	*99.7%*	4,679,869	*99.6%*
All other Oxycodone ER*	5,739,446	*78.8%*	293,717	*5.0%*	36,275	*0.7%*	15,336	*0.3%*	19,285	*0.4%*

* includes products that are not reformulated such as original OxyContin and generic oxycodone ER

Source: IMS Health, National Prescription Audit, Data extracted July 2015.

Table 2. Nationally Estimated Number of Patients Receiving Dispensed Prescriptions for Oxycodone Extended Release (ER) and Oral Solid Formulations of Oxycodone Single-Entity (SE) Immediate-Release (IR), Stratified by Products, from U.S. Outpatient Retail Pharmacies, Years 2005-2014

	2010		2011		2012		2013		2014	
	Patients	*Share*	Patients	*Share*	Patients	*Share*	Patients	*Share*	Patients	*Share*
	N	%	N	%	N	%	N	%	N	%
Total Oxycodone SE IR and ER	4,186,786	*100%*	4,609,862	*100%*	4,845,601	*100%*	4,983,062	*100%*	5,472,416	*100%*
Single-Entity Immediate-Release Formulations	3,306,076	*79.0%*	3,976,613	*86.3%*	4,302,217	*88.8%*	4,489,016	*90.1%*	5,024,973	*91.8%*
Oxycodone SE IR	3,306,076	*100%*	3,976,613	*100%*	4,302,047	*100%*	4,488,748	*100%*	5,024,880	*100%*
Oxecta					294	*0.0%*	433	*0.0%*	206	*0.0%*
Extended-Release Formulations	1,481,740	*35.4%*	1,172,513	*25.4%*	1,077,965	*22.2%*	1,018,434	*20.4%*	975,021	*17.8%*
Reformulated OxyContin	1,318,828	*89.0%*	1,139,297	*97.2%*	1,069,729	*99.2%*	1,015,041	*99.7%*	971,273	*99.6%*
All other Oxycodone ER*	431,365	*29.1%*	103,463	*8.8%*	29,719	*2.8%*	14,365	*1.4%*	15,746	*1.6%*

* includes products that are not reformulated such as original OxyContin and generic oxycodone ER

Note: Unique patient counts may not be added across time periods due to the possibility of double counting those patients who are receiving treatment over multiple periods in the study. Therefore, summing across time periods or drug groups is not advisable and will result in overestimates of patient counts

Source: IMS Health, Total Patient Tracker (TPT), Data extracted May and July, 2015

APPENDIX 2: DATABASES DESCRIPTION

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

IMS Health, Vector One®: Total Patient Tracker (TPT)

The IMS, Vector One®: Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time.

TPT derives its data from the Vector One® database which integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 1.9 billion prescription claims per year, representing over 158 million unique patients. Since 2002 Vector One® has captured information on over 15 billion prescriptions representing over 356 million unique patients.

IMS Health, National Prescription Audit

The National Prescription Audit (NPA™) measures the "retail outflow" of prescriptions, or the rate at which drugs move out of retail pharmacies, mail service houses, or long-term care facilities into the hands of consumers via formal prescriptions in the U.S. The NPA audit measures what is dispensed by the pharmacist. Data for the NPA audit is a national level estimate of the drug activity from retail pharmacies.

NPA™ receives over 2.7 billion prescription claims per year, captured from a sample of the universe of approximately 57,000 pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent nearly 86% of retail prescriptions dispensed nationwide. The type of pharmacies in the sample are a mix of independent, retail, chain, mass merchandisers, and food stores with pharmacies, and include prescriptions from cash, Medicaid, commercial third-party and Medicare Part-D prescriptions. Data is also collected from approximately 40 - 70% (varies by class and geography) of mail service pharmacies and approximately 45-55% of long-term care pharmacies. Data are available on-line for 72- rolling months with a lag of 1 month.

Summary of Clinical Pharmacology Findings:

Purdue Pharma L.P. submitted NDA 206830 to market immediate-release oxycodone HCl tablets (OCI tablet) (5, 10, 15, 20 and 30 mg) for pain management where the use of an opioid analgesic is appropriate.To support the 505(b)(2) NDA, the Applicant has conducted fasted BE study OCI1002, and fed BE study OCI1003 to establish the bioequivalence of the oxycodone HCl tablets to previously approved Roxicodone tablet at 15 mg strength (NDA 021011).
The Applicant evaluated the bioequivalence of OCI tablet with Roxicodone in Study OCI1002, entitled, "A Randomized, Open-Label, Single-Dose, Two-Way Crossover Study in Healthy Subjects to Determine the Fasting Bioequivalence of Abuse-Deterrent Oxycodone Hydrochloride Immediate-Release Tablets (OCI 15 mg) to Roxicodone 15 mg Tablets." Subjects received naltrexone HCl 50 mg tablets (opioid antagonist) with 240 mL of water at –12, 0, 12, and 24 hours relative to each study drug dosing. As indicated in Table 1, mean oxycodone peak plasma concentration (Cmax) and total exposure (AUCt and AUCinf) were similar between OCI 15 mg and Roxicodone 15 mg under fasted conditions. The mean oxycodone Cmax was 34.02 and 38.77 ng/mL for OCI 15 mg and Roxicodone 15 mg, respectively, with a median time to peak exposure (Tmax) of approximately 1 hour. The mean elimination t1/2 of oxycodone was 3.76 and 3.80 hours for OCI 15 mg and Roxicodone 15 mg, respectively.

Table 1: Descriptive Statistics of oxycodone PK parameters following administration of OCI 15 mg tablet or Roxicodone 15 mg tablet while fasting in Study OCI1002.

	OCI 15 mg	**Roxicodone 15 mg**
	N = 51	**N = 53**
AUCt (ng.h/mL)		
Mean	171.39	182.86
SD	45.727	47.787
%CV	26.68	26.13
Min, Max	94.66, 283.91	101.45, 303.53
AUCinf (ng.h/mL)		
Mean	172.84	184.35
SD	45.772	47.64
%CV	26.48	25.84
Min, Max	97.85, 285.15	106.07, 304.57
Cmax (ng/mL)		
Mean	34.02	38.77
SD	11.234	10.919
%CV	33.02	28.16
Min, Max	15.0, 69.7	23.8, 73.2
Tmax (h)		
Median	1.03	1.00
Min, Max	0.50, 5.00	0.50, 6.07

The 90% confidence intervals (CIs) were estimated for the ratio (test/reference) by exponentiating the CI for the difference in least-squares (LS) means of log transformed data. Bioequivalence (test versus reference) would be established if the 90% CIs fell within the range of 80% to 125%. Statistical analysis indicated that the Cmax, AUCt, AUCinf for oxycodone from OCI 15 mg tablet was bioequivalent to Roxicodone 15 mg tablet (See table 2 below). Additionally, partial AUC's of oxycodone over the typical dosing regimen (about 4 to 6 hours) were compared for both the product. Based on the 90% CI interval bounds the partial AUC ratios of OCI 15 mg tablet appear to be bioequivalent with Roxicodone 15 mg tablet four hours following administration.

Table 2: Statistical Analysis: Plasma Pharmacokinetic Metrics of Oxycodone HCl in the Fasted State (OCI1002).

	LS Geometric Means[a]				
Metric (unit)	**OCI 15 mg**	**Roxicodone 15 mg**	**CV (%)**	**LS Mean Ratio (%) (OCI/Roxicodone)[b]**	**90% CI of Ratio[c]**
AUCt (h*ng/mL)	165	177	8.79	93.6	90.9, 96.4
AUCinf (h*ng/mL)	167	178	8.50	93.6	91.0, 96.3
Cmax (ng/mL)	32.3	37.4	19.6	86.3	81.0, 92.1

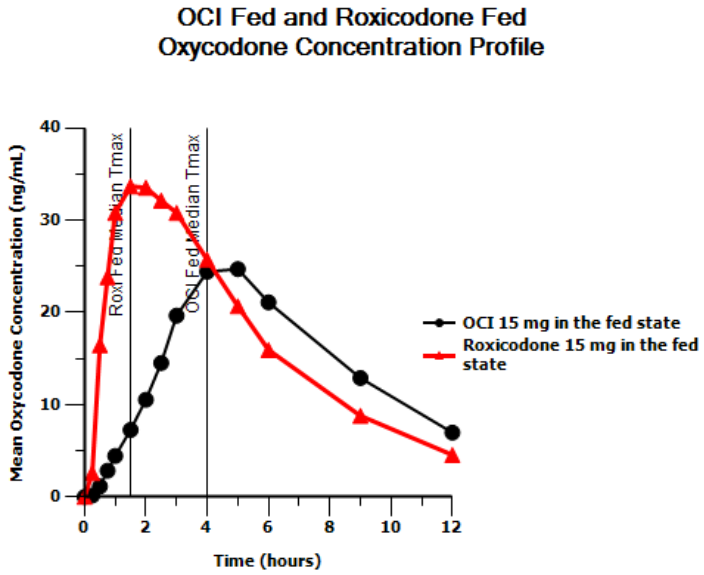
However, in the fed bioequivalence study OCI1003, significant food-effect related delay in Tmax was noted. Study OCI1003 was "A Randomized, Open-Label, Single-Dose, Two-Way Crossover Study in Healthy Subjects (N=55) to Determine the Fed Bioequivalence of Abuse-Deterrent Oxycodone Hydrochloride Immediate-Release Tablets (OCI 15 mg) to Roxicodone 15 mg Tablets". In order to block the opioid effects, subjects received naltrexone HCl 50 mg tablets (opioid antagonist) with 240 mL of water at –12, 0, 12, and 24 hours relative to each study drug dosing.

Table 3: Descriptive Statistics of oxycodone PK parameters following administration of OCI 15 mg tablet or Roxicodone 15 mg tablet under fed condition in Study OCI1003

Table 3	OCI 15 mg	Roxicodone 15 mg
	N = 51	**N = 53**
AUCt (ng.h/mL)		
Mean	226.49	241.24
SD	60.543	61.346
%CV	26.73	25.43
Min, Max	103.16, 368.09	107.06, 359.34
AUCinf (ng.h/mL)		
Mean	227.96	242.75
SD	60.34	61.283
%CV	26.47	25.24
Min, Max	105.00, 369.46	107.78, 360.94
Cmax (ng/mL)		
Mean	29.79	41.43
SD	7.177	11.743
%CV	24.09	28.35
Min, Max	18.4, 47.4	22.0, 82.5
Tmax (h)		
Median	4.00	1.50
Min, Max	1.00, 9.05	0.50, 4.05

As indicated in Table 3, the mean Cmax was 29.79 ng/mL and 41.43 ng/mL for OCI and Roxicodone under fed condition, respectively, indicating a 27% lower Cmax with OCI. Median time to peak exposure (Tmax) was approximately 4 hours (Range: 1 to 9 hours) for OCI and approximately 1.5 hours (Range: 0.5 – 4 hours) for Roxicodone. The mean elimination $t_{1/2}$ of oxycodone was 4.13 and 4.18 hours for OCI 15 mg and Roxicodone 15 mg, respectively. Mean oxycodone total exposure (AUCt and AUCinf) was similar for OCI 15 mg and Roxicodone 15 mg under fed conditions.

Figure 1: Pharmacokinetic profile of oxycodone following administration of OCI tablet or Roxicodone with FDA high fat meal.



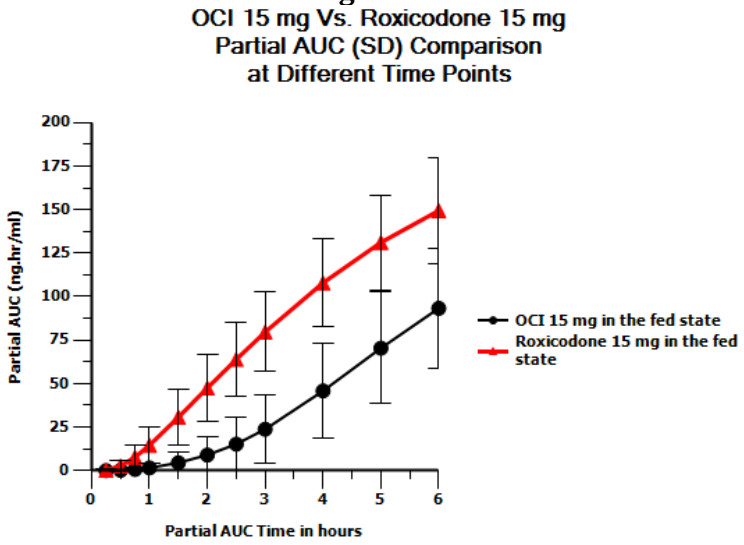
The 90% confidence intervals (CIs) were estimated for the ratio (test/reference) by exponentiating the CI for the difference in least-squares (LS) means of log transformed data. Bioequivalence (test versus reference) would be established if the 90% CIs fell within the range of 80% to 125%. Statistical analysis indicated that the AUCt, AUCinf for oxycodone from OCI 15 mg tablet was bioequivalent to Roxicodone 15 mg tablet, except Cmax (Table 4). As mentioned before, mean Cmax of oxycodone with OCI tablet is 27% lower compared to Roxicodone under fed condition. Considering the full 36 hour profile of blood sampling, AUCinf of OCI tablet met the bioequivalence criteria to Roxicodone.

Table 4: Statistical Analysis of Oxycodone Pharmacokinetic Metrics in Fed BE Study OCI1003.

	LS Geometric Means[a]				
Metric (unit)	**OCI 15 mg**	**Roxicodone 15 mg**	**CV (%)**	**LS Mean Ratio (%) (OCI/Roxicodone)[b]**	**90% CI of Ratio[c]**
AUCt (h*ng/mL)	218	234	7.74	93.4	91.1, 95.9
AUCinf (h*ng/mL)	220	235	7.69	93.5	91.1, 95.9
Cmax (ng/mL)	28.9	39.8	18.0	72.6	68.4, 77.0

Since the range of Tmax for OCI 15 mg tablet was found to be much wider (1 – 9 hours) compared to Roxicodone 15 mg tablet (0.5 – 4 hours), partial AUC's of oxycodone were compared for both the products (See Figure 2 below). Over the duration of a typical dosing interval (4 to 6 hours), OCI 15 mg tablet resulted in a consistently lower systemic exposure (partial AUC) of oxycodone compared to Roxicodone 15 mg tablet under fed condition.

Figure 2: Partial AUC profile of oxycodone following administration of OCI tablet or Roxicodone with FDA high fat meal.

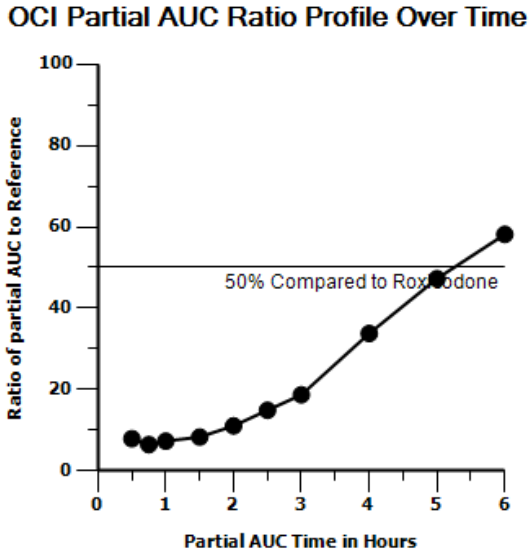


Further comparison of the Cmax and partial AUC's of OCI tablet indicated a systematic delay in absorption of oxycodone compared to Roxicodone (See Table 5 below). A typical dosing interval of oxycodone immediate-release formulation is around 4 to 6 hours. As shown in Table 5 and Figure 3, oxycodone exposure with OCI, in terms of partial AUC comparison, is less than 50% of Roxicodone over the first 4 hours, later approaching a ratio of 60% around 6 hours. This clearly indicates that oxycodone release and absorption is delayed significantly following administration of OCI tablet with food.

Table 5: Comparison of OCI Cmax, AUC and Partial AUC's with reference to Roxicodone from Fed BE study OCI1003.

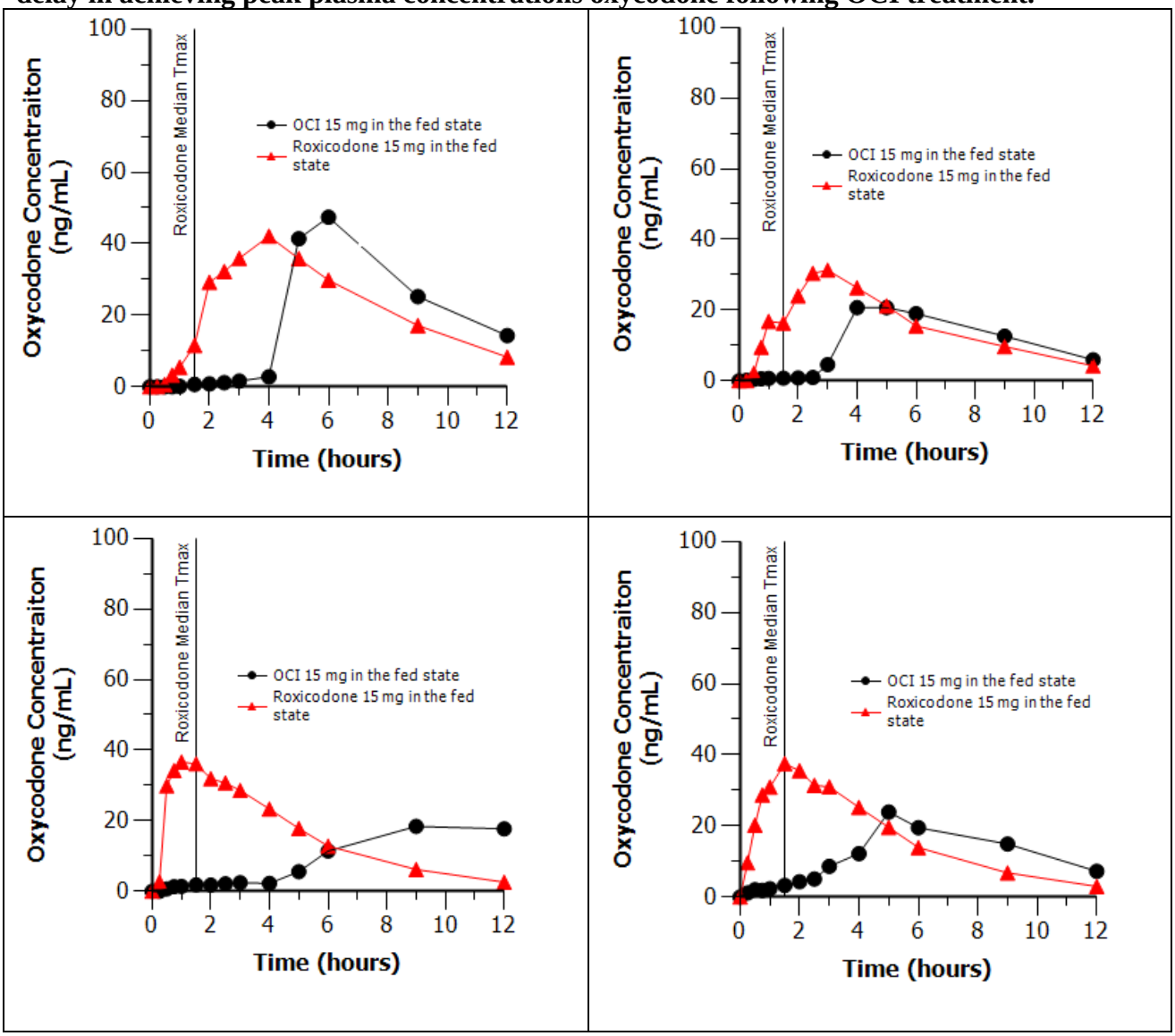
Parameter	Ratio % Reference	Lower 90%CI	Upper 90%CI
Cmax	72.6	68.3	77.0
AUC0-0.25	21.0	12.7	34.7
AUC0-0.5	8.1	5.5	12.0
AUC0-0.75	6.6	4.1	10.6
AUC0-1	7.5	5.0	11.2
AUC0-1.5	8.4	5.8	12.2
AUC0-2	11.3	8.1	15.6
AUC0-2.5	15.3	11.4	20.4
AUC0-3	19.1	14.2	25.8
AUC0-4	35.0	29.2	42.0
AUC0-5	49.1	42.9	56.1
AUC0-6	60.0	54.3	66.2
AUCinf	93.5	91.1	95.9

Figure 3: Profile of partial AUC ratios of OCI tablet to Roxicodone over the duration of a typical dosing interval under fed condition (4 to 6 hours).



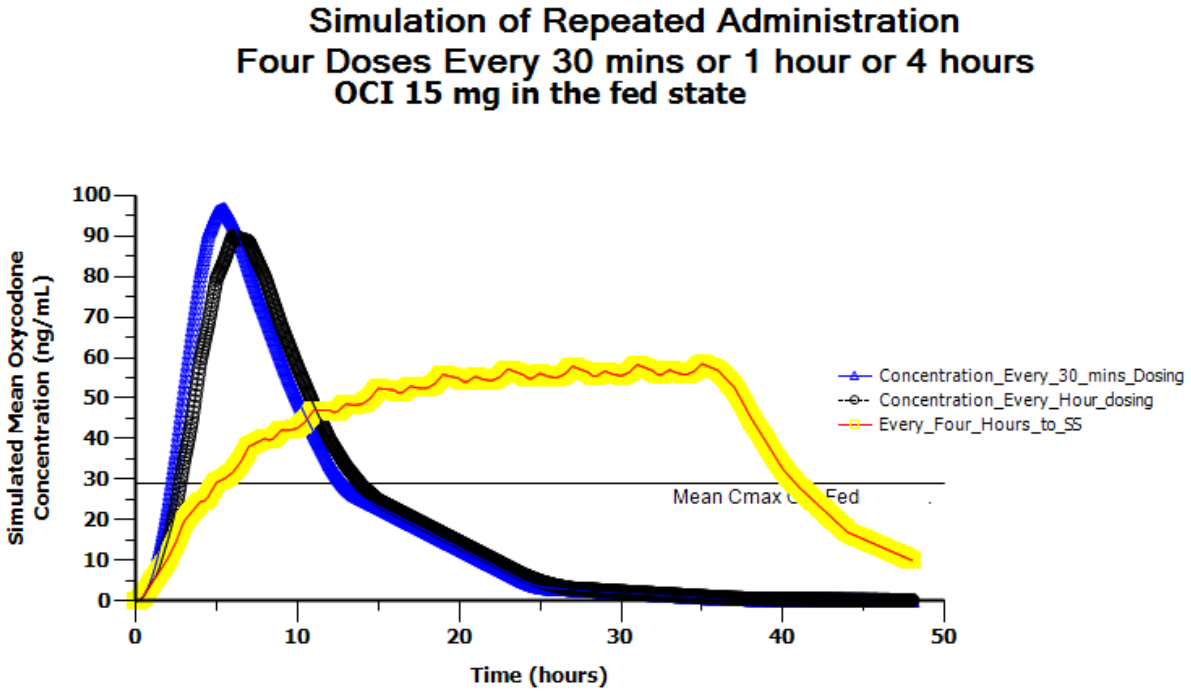
The Applicant acknowledged that the median Tmax was delayed approximately 2.5 hours following the administration of OCI 15 mg tablets compared with the administration of Roxicodone 15 mg tablets. However, the Applicant also indicated in the proposed product label 12.3 Clinical Pharmacology, Food Effect section that "These differences in oxycodone pharmacokinetics are not clinically relevant and OCI tablet can be taken without regard to food". Representative plots of PK profiles from four subjects with the largest delay in Tmax are shown in Figure 4.

Figure 4: Examples of oxycodone PK profiles from four subjects that had a prolonged delay in achieving peak plasma concentrations oxycodone following OCI treatment.



Currently marketed oxycodone immediate-release products do not have significant food effects that warrant a dietary restriction around taking the medication as needed (usually every 4 to 6 hours). This 505(b)(2) NDA refers to safety and efficacy information described in the reference product label for Roxicodone Tablets (NDA 021011). Both Roxicodone tablet and oral solution product labels describe a food effect study conducted in healthy subjects using 5 mg/5 mL oral solution, where the product label indicates the following: "…food caused a delay in Tmax (1.25 to 2.54 hour). Similar effects of food are expected with the 15 mg and 30 mg tablets".
The proposed product is indicated for acute pain management. A patient taking OCI tablet with food with a delay in absorption, may attempt to achieve pain relief by taking one or more additional doses before the label-recommended dosing interval. Hence, a simulation of repeated administration of four consecutive doses within every 30 minutes, every 1 hour, or after every 4 hours was conducted based on the single-dose profile of the subjects from fed BE study OCI1003. This simulation (shown in Figure 5 below) is a worst case scenario and assumes dosing that is outside of normal recommendation of labeling for an opioid.

Figure 5: Nonparametric simulation of mean oxycodone concentration profile following repeated administration of OCI (fed state) every 30 mins, or 1 hour or every 4 hours.



In addition, it is not clear if the delay in Tmax would be observed with other types of meals compared to the observed food effect with the FDA high fat high calorie meal employed in study OCI1003. Other meal types could be composed of medium fat medium calorie, low fat low calorie, etc; which may result in a different magnitude of delay in Tmax.

For an IR product based on a 505(b)(2) pathway to establish bioequivalence with a reference product, conducting a fasted BE study and a food-effect study is recommended in the draft Guidance for Industry on Bioavailability and Bioequivalence (BA/BE). If a significant food effect is noted, it is important to understand the nature of the food effect on the concentration vs. time profile. A fed BE study can help evaluate the food effect and similarity of pharmacokinetic profile between test and reference products.

Guidance for Industry

Food-Effect Bioavailability and Fed Bioequivalence Studies

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2002
BP

Guidance for Industry

Food-Effect Bioavailability and Fed Bioequivalence Studies

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Guidance For Industry[1]

Food-Effect Bioavailability and Fed Bioequivalence Studies

This guidance represents the Food and Drug Administration=s current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

I. INTRODUCTION

This guidance provides recommendations to sponsors and/or applicants planning to conduct food-effect bioavailability (BA) and fed bioequivalence (BE) studies for orally administered drug products as part of investigational new drug applications (INDs), new drug applications (NDAs), abbreviated new drug applications (ANDAs), and supplements to these applications. This guidance applies to both immediate-release and modified-release drug products. The guidance addresses how to meet the BA and BE requirements in 21 CFR 320, 314.50 (d) (3), and 314.94 (a) (7) as they apply to oral dosage forms. This guidance provides recommendations for food-effect BA and fed BE study designs, data analysis, and product labeling. It also provides information on when food-effect BA and fed BE studies should be performed. [2]

II. BACKGROUND

Food effect BA studies are usually conducted for new drugs and drug products during the IND period to assess the effects of food on the rate and extent of absorption of a drug when the drug product is administered shortly after a meal (fed conditions), as compared to administration under fasting conditions. Fed BE studies, on the other hand, are conducted for ANDAs to demonstrate their bioequivalence to the reference listed drug (RLD) under fed conditions.

A. Potential Mechanisms of Food Effects on BA

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[1] This guidance has been prepared by the Food Effect Working Group of the Biopharmaceutics Coordinating Committee in the Office of Pharmaceutical Science, Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA).

[2] See also the guidance for industry on *Bioavailablity and Bioequivalence Studies for Orally Administered Drug Products C General Considerations*.

Food can change the BA of a drug and can influence the BE between test and reference products. Food effects on BA can have clinically significant consequences. Food can alter BA by various means, including

- Delay gastric emptying
- Stimulate bile flow
- Change gastrointestinal (GI) pH
- Increase splanchnic blood flow
- Change luminal metabolism of a drug substance
- Physically or chemically interact with a dosage form or a drug substance

Food effects on BA are generally greatest when the drug product is administered shortly after a meal is ingested. The nutrient and caloric contents of the meal, the meal volume, and the meal temperature can cause physiological changes in the GI tract in a way that affects drug product transit time, luminal dissolution, drug permeability, and systemic availability. In general, meals that are high in total calories and fat content are more likely to affect the GI physiology and thereby result in a larger effect on the BA of a drug substance or drug product. We recommend use of high-calorie and high-fat meals during food-effect BA and fed BE studies.

B. Food Effects on Drug Products

Administration of a drug product with food may change the BA by affecting either the drug substance or the drug product. In practice, it is difficult to determine the exact mechanism by which food changes the BA of a drug product without performing specific mechanistic studies. Important food effects on BA are least likely to occur with many rapidly dissolving, immediate-release drug products containing highly soluble and highly permeable drug substances (BCS Class I) because absorption of the drug substances in Class I is usually pH- and site-independent and thus insensitive to differences in dissolution.[3] However, for some drugs in this class, food can influence BA when there is a high first-pass effect, extensive adsorption, complexation, or instability of the drug substance in the GI tract. In some cases, excipients or interactions between excipients and the food-induced changes in gut physiology can contribute to these food effects and influence the demonstration of BE. For rapidly dissolving formulations of BCS Class I drug substances, food can affect C_{max} and the time at which this occurs (T_{max}) by delaying gastric emptying and prolonging intestinal transit time. However, we expect the food effect on these measures to be similar for test and reference products in fed BE studies.

For other immediate-release drug products (BCS Class II, III, and IV) and for all modified-release drug products, food effects are most likely to result from a more complex combination of factors that influence the in vivo dissolution of the drug product and/or the absorption of the drug substance. In these cases, the relative direction and magnitude of food effects on formulation BA and the effects on the demonstration of BE are difficult, if not impossible, to predict without conducting a fed BE study.

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[3] See the guidance for industry on *Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System*.

III. RECOMMENDATIONS FOR FOOD-EFFECT BA AND FED BE STUDIES

This section of the guidance provides recommendations on when food-effect BA studies should be conducted as part of INDs and NDAs and when fed BE studies should be conducted as part of ANDAs. For postapproval changes in an approved immediate- or modified-release drug product that requires in vivo redocumentation of BE under fasting conditions, fed BE studies are generally unnecessary.

A. Immediate-Release Drug Products

1. INDs/NDAs

We recommend that a food-effect BA study be conducted for all new chemical entities (NCEs) during the IND period.

Food-effect BA studies should be conducted early in the drug development process to guide and select formulations for further development. Food-effect BA information should be available to design clinical safety and efficacy studies and to provide information for the CLINICAL PHARMACOLOGY and/or DOSAGE AND ADMINISTRATION sections of product labels. If a sponsor makes changes in components, composition, and/or method of manufacture in the clinical trial formulation prior to approval, BE should be demonstrated between the to-be-marketed formulation and the clinical trial formulation.

Sponsors may wish to use relevant principles described in the guidance for industry on *SUPAC-IR: Immediate Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation* (SUPAC-IR guidance) to determine if in vivo BE studies are recommended. These BE studies, if indicated, should generally be conducted under fasting conditions.

2. ANDAs

In addition to a BE study under fasting conditions, we recommend a BE study under fed conditions for all orally administered immediate-release drug products, with the following exceptions:

- When both test product and RLD are rapidly dissolving, have similar dissolution profiles, and contain a drug substance with high solubility and high permeability (BCS Class I) (see footnote 3), or

- When the DOSAGE AND ADMINISTRATION section of the RLD label states that the product should be taken only on an empty stomach, or

- When the RLD label does not make any statements about the effect of food on absorption or administration.

B. Modified-Release Drug Products

We recommend that food-effect BA and fed BE studies be performed for all modified-release dosage forms.

1. INDs/NDAs

We recommend a study comparing the BA under fasting and fed conditions for all orally administered modified-release drug products.

When changes occur in components, composition, and/or method of manufacture between the to-be-marketed formulation and the primary clinical trial material, the sponsor may wish to use relevant principles described in the guidance for industry on *SUPAC-MR: Modified Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing, and Controls: In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation* (SUPAC-MR guidance) to determine if documentation of in vivo BE is recommended. These BE studies, if indicated, should generally be conducted under fasting conditions.

2. ANDAs

In addition to a BE study under fasting conditions, a BE study under fed conditions should be conducted for all orally administered modified-release drug products.

IV. STUDY CONSIDERATIONS

This section provides general considerations for designing food effect BA and fed BE studies. A sponsor may propose alternative study designs and data analyses. The scientific rationale and justification for these study designs and analyses should be provided in the study protocol. Sponsors may choose to conduct additional studies for a better understanding of the drug product and to provide optimal labeling statements for dosage and administration (e.g. different meals and different times of drug intake in relation to meals). In studying modified-release dosage forms, consideration should be given to the possibility that co-administration with food can result in *dose dumping*, in which the complete dose may be more rapidly released from the dosage form than intended, creating a potential safety risk for the study subjects.

A. General Design

We recommend a randomized, balanced, single-dose, two-treatment (fed vs. fasting), two-period, two-sequence crossover design for studying the effects of food on the BA of either an immediate-release or a modified-release drug product. The formulation to be tested should be administered on an empty stomach (fasting condition) in one period and following a test meal

(fed condition) in the other period. We recommend a similar, two-treatment, two-period, two-sequence crossover design for a fed BE study except that the treatments should consist of both test and reference formulations administered following a test meal (fed condition). An adequate washout period should separate the two treatments in food-effect BA and fed BE studies.

B. Subject Selection

Both food-effect BA and fed BE studies can be carried out in healthy volunteers drawn from the general population. Studies in the patient population are also appropriate if safety concerns preclude the enrollment of healthy subjects. A sufficient number of subjects should complete the study to achieve adequate power for a statistical assessment of food effects on BA to claim an absence of food effects, or to claim BE in a fed BE study (see DATA ANALYSIS AND LABELING section). A minimum of 12 subjects should complete the food-effect BA and fed BE studies.

C. Dosage Strength

In general, the highest strength of a drug product intended to be marketed should be tested in food-effect BA and fed BE studies. In some cases, clinical safety concerns can prevent the use of the highest strength and warrant the use of lower strengths of the dosage form. For ANDAs, the same lot and strength used in the fasting BE study should be tested in the fed BE study. For products with multiple strengths in ANDAs, if a fed BE study has been performed on the highest strength, BE determination of one or more lower strengths can be waived based on dissolution profile comparisons (for details see the guidance on *Bioavailablity and Bioequivalence Studies for Orally Administered Drug Products - General Considerations.*

D. Test Meal

We recommend that food-effect BA and fed BE studies be conducted using meal conditions that are expected to provide the greatest effects on GI physiology so that systemic drug availability is maximally affected. A high-fat (approximately 50 percent of total caloric content of the meal) and high-calorie (approximately 800 to 1000 calories) meal is recommended as a test meal for food-effect BA and fed BE studies. This test meal should derive approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively.[4] The caloric breakdown of the test meal should be provided in the study report. If the caloric breakdown of the meal is significantly different from the one described above, the sponsor should provide a scientific rationale for this difference. In NDAs, it is recognized that a sponsor can choose to conduct food-effect BA studies using meals with different combinations of fats, carbohydrates, and proteins for exploratory or label purposes. However, one of the meals for the food-effect BA studies should be the high-fat, high-calorie test meal described above.

[4] An example test meal would be two eggs fried in butter, two strips of bacon, two slices of toast with butter, four ounces of hash brown potatoes and eight ounces of whole milk. Substitutions in this test meal can be made as long as the meal provides a similar amount of calories from protein, carbohydrate, and fat and has comparable meal volume and viscosity.

E. Administration

Fasted Treatments: Following an overnight fast of at least 10 hours, subjects should be administered the drug product with 240 mL (8 fluid ounces) of water. No food should be allowed for at least 4 hours post-dose. Water can be allowed as desired except for one hour before and after drug administration. Subjects should receive standardized meals scheduled at the same time in each period of the study.

Fed Treatments: Following an overnight fast of at least 10 hours, subjects should start the recommended meal 30 minutes prior to administration of the drug product. Study subjects should eat this meal in 30 minutes or less; however, the drug product should be administered 30 minutes after start of the meal. The drug product should be administered with 240 mL (8 fluid ounces) of water. No food should be allowed for at least 4 hours post-dose. Water can be allowed as desired except for one hour before and after drug administration. Subjects should receive standardized meals scheduled at the same time in each period of the study.

F. Sample Collection

For both fasted and fed treatment periods, timed samples in biological fluid, usually plasma, should be collected from the subjects to permit characterization of the complete shape of the plasma concentration-time profile for the parent drug. It may be advisable to measure other moieties in the plasma, such as active metabolites, and sponsors should refer to the guidance on *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations* for recommendations on these issues. Consideration should be given to the possibility that co-administration of a dosage form with food can alter the time course of plasma drug concentrations so that fasted and fed treatments can have different sample collection times.

V. DATA ANALYSIS AND LABELING

Food-effect BA studies may be exploratory and descriptive, or a sponsor may want to use a food-effect BA study to make a label claim.[5] The following exposure measures and pharmacokinetic parameters should be obtained from the resulting concentration-time curves for the test and reference products in food-effect BA and fed BE studies:

- Total exposure, or area under the concentration-time curve ($AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$)
- Peak exposure (C_{max})
- Time to peak exposure (T_{max})
- Lag-time (t_{lag}) for modified-release products, if present
- Terminal elimination half-life
- Other relevant pharmacokinetic parameters

Individual subject measurements, as well as summary statistics (e.g., group averages, standard deviations, coefficients of variation) should be reported. An equivalence approach is

[5] Regulations on labeling requirements for a drug product submitted in an NDA can be found in 21 CFR part 201.

recommended for food-effect BA (to make a claim of no food effects) and fed BE studies, analyzing data using an average criterion. Log-transformation of exposure measurements (AUC and C_{max}) prior to analysis is recommended. The 90 percent CI for the ratio of population geometric means between test and reference products should be provided for $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, and C_{max} (see guidance for industry on *Statistical Approaches to Establishing Bioequivalence*). For IND or NDA food-effect BA studies, the fasted treatment serves as the reference. For ANDA fed BE studies, the RLD administered under fed condition serves as the reference treatment.

The effect of food on the absorption and BA of a drug product should be described in the CLINICAL PHARMACOLOGY section of the labeling. In addition, the DOSAGE AND ADMINISTRATION section of the labeling should provide instructions for drug administration in relation to food based on clinical relevance (i.e., whether or not the changes in systemic exposure caused by co-administration with food results in safety or efficacy concerns, or when there is no important change in systemic exposure but there is a possibility that the drug substance causes GI irritation when taken without food).

For an NDA, an absence of food effect on BA is not established if the 90 percent CI for the ratio of population geometric means between fed and fasted treatments, based on log-transformed data, is not contained in the equivalence limits of 80-125 percent for either $AUC_{0\text{-}inf}$ ($AUC_{0\text{-}t}$ when appropriate) or C_{max}. When the 90 percent CI fails to meet the limits of 80-125 percent, the sponsor should provide specific recommendations on the clinical significance of the food effect based on what is known from the total clinical database about dose-response (exposure-response) and/or pharmacokinetic-pharmacodynamic relationships of the drug under study. The clinical relevance of any difference in T_{max} and t_{lag} should also be indicated by the sponsor. The results of the food-effect BA study should be reported factually in the CLINICAL PHARMACOLOGY section of the labeling and should form the basis for making label recommendations (e.g., *take only on an empty stomach*) in the DOSAGE AND ADMINISTRATION section of the labeling. The following are examples of language for the package insert:

> A food-effect study involving administration of [the drug product] to healthy volunteers under fasting conditions and with a high-fat meal indicated that the C_{max} and AUC were increased 57% and 45%, respectively, under fed conditions. This increase in exposure can be clinically significant, and therefore [the drug] should be taken only on an empty stomach (1 hour before or 2 hours after a meal)

> A food-effect study involving administration of [the drug product] to healthy volunteers under fasting conditions and with a high-fat meal indicated that the C_{max} was decreased 15% while the AUC remained unchanged. This decrease in exposure is not clinically significant, and therefore [the drug] could be taken without regards to meals.

An absence of food effect on BA is indicated when the 90 percent CI for the ratio of population geometric means between fed and fasted treatments, based on log-transformed data, is contained in the equivalence limits of 80-125 percent for $AUC_{0\text{-}inf}$ ($AUC_{0\text{-}t}$ when appropriate) and C_{max}. In this case, a sponsor can make a specific claim in the CLINICAL PHARMACOLOGY or DOSAGE AND ADMINISTRATION section of the label that no food effect on BA is expected

provided that the T_{max} differences between the fasted and fed treatments are not clinically relevant. The following is an example of language for the package insert:

> The C_{max} and AUC data from a food-effect study involving administration of [the drug product] to healthy volunteers under fasting conditions and with a high-fat meal indicated that exposure to the drug is not affected by food. Therefore, [the drug product] may be taken without regard to meals.

For an ANDA, BE of a test product to the RLD product under fed conditions is concluded when the 90 percent CI for the ratio of population geometric means between the test and RLD product, based on log-transformed data, is contained in the BE limits of 80-125 percent for AUC and C_{max}. Although no criterion applies to T_{max}, the T_{max} values for the test and reference products are expected to be comparable based on clinical relevance. The conclusion of BE under fed conditions indicates that with regard to food, the language in the package insert of the test product can be the same as the reference product.

VI. OTHER CONSIDERATIONS

A. Sprinkles

In NDAs, the labeling of certain drug products (e.g., controlled-release capsules containing beads) can recommend that the product be sprinkled on soft foods, such as applesauce, and swallowed without chewing. For the labeling to indicate that the drug product can be sprinkled on soft foods, additional in vivo relative BA studies should be performed by sprinkling the product on the soft foods to be listed in the labeling (test treatment) and comparing it to the product administered in the intact form (reference treatment), then administering both on an empty stomach.

In ANDAs, BE of the test to the RLD is demonstrated in a single dose crossover study. Both treatments should be sprinkled on one of the soft foods mentioned in the labeling, usually applesauce. The BE data should be analyzed using average BE and the 90 percent CI criteria should be used to declare BE. If there are questions about other foods, the design, or the analysis of such BE studies, the sponsors and/or applicants should contact the Office of Generic Drugs.

B. Special Vehicles

For NDAs, the labeling for certain oral solution products (e.g., cyclosporine oral solution, modified) recommends that the solution be mixed with a beverage prior to administration. The BA of these products can change when mixed with different beverages due to the formation of complex mixtures and other physical-chemical and/or physiological factors. NDA sponsors should contact the Office of Clinical Pharmacology and Biopharmaceutics to determine what data should be submitted to support labeling.

In ANDAs, BE of the test to the RLD is demonstrated in a single-dose crossover study. Both treatments should be mixed with one of the beverages mentioned in the labeling. Sponsors

should provide evidence that BE differences would not be expected from the use of other listed vehicles. The BE data should be analyzed using average BE, and the 90 percent CI criteria should be used to declare BE. If there are questions about other vehicles, or the design or analysis of such BE studies, the sponsors and/or applicants should contact the Office of Generic Drugs.

Guidance for Industry

Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs — General Considerations

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact the CDER Office of Clinical Pharmacology at 301-796-5008 or OCP@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

March 2014
Biopharmaceutics

Guidance for Industry

Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs—General Considerations

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Food and Drug Administration
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Guidance for Industry[1]

Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs — General Considerations

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance provides recommendations to sponsors and/or applicants planning to include bioavailability (BA) and bioequivalence (BE) information for drug products in investigational new drug applications (INDs), new drug applications (NDAs), and NDA supplements (referred to as the NDA BA and BE Draft Guidance).[2] This guidance contains advice on how to meet the BA and BE requirements set forth in 21 CFR part 320 as they apply to dosage forms intended for oral administration.[3] The guidance may also be applicable to non-orally administered drug products when reliance on systemic exposure measures is suitable to document BA and BE (e.g., transdermal delivery systems and certain rectal and nasal drug products). The guidance should be helpful for applicants conducting BA and BE studies during the IND period for an NDA and also for applicants conducting BE studies during the postapproval period for certain changes to

[1] This guidance was developed by the Office of Clinical Pharmacology, Office of Translational Sciences, and the Office of New Drugs Quality Assessment, Office of Pharmaceutical Science, in the Center for Drug Evaluation and Research (CDER) at the U.S. Food and Drug Administration (FDA).

[2] BA and BE information for drug products in abbreviated new drug applications (ANDAs) and ANDA supplements are not the subject of this guidance. FDA has issued a separate draft guidance on this topic entitled *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA* (December 2013) (ANDA BE Draft Guidance). The ANDA BE Draft Guidance, when finalized, will represent FDA's current thinking on this topic. Many guidances are referenced throughout this document. The guidance referred to in this footnote, as well as others referenced throughout the remainder of the document, can be found on the FDA Drugs guidance Web page at http://www fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default htm. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page.

[3] These dosage forms include tablets, capsules, solutions, suspensions, conventional/immediate-release drug products, and modified (extended, delayed)-release drug products.

drug products that are the subject of an NDA.[4] This guidance document is not intended to provide recommendations on studies conducted in support of demonstrating comparability or biosimilarity for biological products licensed under section 351 of the Public Health Service Act.[5]

When finalized, this guidance will revise and replace the parts of FDA's March 2003 guidance for industry on *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations* (the March 2003 BA and BE Guidance) relating to BA and BE studies for INDs, NDAs, and NDA supplements.[6] Since the March 2003 BA and BE Guidance was issued, FDA has determined that providing information on BA and BE studies in separate guidances according to application type will be beneficial to sponsors and applicants. Thus, FDA is issuing this NDA BA and BE Draft Guidance and, as previously noted, has issued the ANDA BE Draft Guidance for ANDA and ANDA supplements.[7]

We recognize that this guidance cannot address every issue pertaining to the assessment of BA or BE studies for INDs and NDAs, so we suggest sponsors and applicants contact the appropriate review division for guidance on specific questions not addressed by this guidance.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance documents means that something is suggested or recommended, but not required.

II. BACKGROUND

[4] *Bioequivalence* is a statutory term reflected in the Federal Food, Drug, and Cosmetic Act (FD&C Act) in section 505(j) (21 U.S.C. 355(j)), which requires ANDA applicants to demonstrate, among other things, that the proposed generic product is bioequivalent to its reference listed drug. Section 505(j)(2)(A)(iv) of the FD&C Act; see also section 505(j)(8) of the FD&C Act. There is no similar statutory requirement for an NDA applicant either under section 505(b)(1) or (b)(2) of the FD&C Act to demonstrate bioequivalence of its proposed product to another product. As a scientific matter, however, the same or a similar showing of the bioavailability of two products in the NDA context may be needed for the purposes of evaluating the safety or effectiveness of a product. For ease of the reader, we refer to such evaluations of the relative bioavailability for two or more products as an evaluation of bioequivalence in this guidance.

[5] For information on these types of studies, see FDA's Drugs guidance Web page. See footnote #2 for information on accessing this Web page.

[6] Revisions to the March 2003 BA and BE Guidance include (1) expansion of the section on modified-release products, (2) addition of a section on concomitant administration of drug products and combination drug products, (3) addition of a section on alcoholic beverage effects on modified-release dosage forms, (4) addition of an endogenous substance section, (5) addition of a section on drug products with high intrasubject variability, and (6) removal of references to BE studies conducted for ANDAs. The guidance also makes other revisions for clarification.

[7] See footnote #2.

BA assessment of formulations is a component of new drug development. The approaches of evaluating BA and BE discussed in this guidance are designed to aid FDA evaluation of the safety and effectiveness of a product that is the subject of an IND, NDA, or NDA supplement. In this endeavor, we use the totality of information available in the submission, which includes, among other things, information gathered using the principles of BE, exposure-response evaluations, and clinical trial results. The evaluation of BE in the generic drug context, by contrast, is used to support a determination that a generic product may be substituted for its reference listed drug, and involves consideration of different types of data permitted in an ANDA. Accordingly, the approaches discussed in this guidance may differ from similar discussions of BE in the ANDA BE Draft Guidance. For example, this NDA BA and BE Draft Guidance recommends assessment of the effect of food on BA using the approaches set forth in FDA's 2002 guidance for industry on *Food-Effect Bioavailability and Fed Bioequivalence Studies* (the 2002 Food-Effect Guidance). Fasting BE studies generally are sufficient, given the totality of information we consider in evaluating INDs, NDAs, or NDA supplements. In contrast, we recommend in the ANDA BE Draft Guidance fed and fasting BE studies that will provide specific information to support a demonstration of BE under section 505(j) of the FD&C Act, and in turn, to support substitutability. Even though the ANDA BE Draft Guidance revises and replaces the parts of the 2002 Food-Effect Guidance pertaining to ANDAs and ANDA supplements, this NDA BA and BE Draft Guidance does not replace the 2002 Food-Effect Guidance relating to studies for INDs, NDAs, and NDA supplements.[8]

A. General

Studies to measure BA and/or establish BE of a product are important elements in support of INDs, NDAs, and NDA supplements. *Bioavailability* means the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action (21 CFR 320.1(a)). BA data provide an estimate of the fraction of the drug absorbed, as well as provide information related to the pharmacokinetics of the drug.

Bioequivalence means the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives become available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study (21 CFR 320.1(e)). Studies to establish BE between two products are important for certain formulation or manufacturing changes occurring during the drug development and postapproval stages. In BE studies, the exposure profile of a test drug product is compared to that of a reference drug product.

B. Bioavailability

BA for a given formulation provides an estimate of the relative fraction of the orally administered dose that is absorbed into the systemic circulation. BA for orally administered drug products can be documented by comparing a systemic exposure profile to that of a suitable reference product. A profile can be generated by measuring the concentration of active

[8] Accordingly, we are in the process of revising the 2002 Food-Effect Guidance.

ingredients and/or active moieties over time and, when appropriate, active metabolites over time in samples collected from the systemic circulation. Systemic exposure profiles reflect both release of the drug substance from the drug product and a series of possible presystemic/systemic actions on the drug substance after its release from the drug product.

FDA's regulations at 21 CFR 320.25 set forth guidelines for in vivo BA studies. As provided in this regulation, the reference product for BA studies should be a solution, suspension, or intravenous (IV) dosage form (21 CFR 320.25(d)(2) and (3)). The purpose of conducting a BA study with an oral solution as a reference is to assess the impact of formulation on BA. Conducting a BA study with an IV reference enables assessment of the impact of route of administration on BA and defines the absolute BA of the drug released from the drug product.

C. Bioequivalence

As noted previously, both BA and BE focus on the release of a drug substance from a drug product and subsequent absorption into systemic circulation. As a result, we recommend that approaches to determining BE generally follow approaches similar to those used for BA. Demonstrating BE involves a more formal comparative test that uses specific references with specified criteria for comparisons and predetermined BE limits for such criteria.

1. Preapproval Changes

BE documentation can be useful during the IND period to compare (1) early and late clinical trial formulations; (2) formulations used in clinical trials and stability studies, if different; (3) clinical trial formulations and to-be-marketed drug products, if different; and (4) product strength equivalence, as appropriate. In each comparison, the new formulation, formulation produced by the new method of manufacture, or new strength is the candidate, or test product and the prior formulation, prior method of manufacture, or prior strength is the reference product. The decision to document BE during drug development is generally left to the judgment of the sponsor, using the principles of relevant guidances (in this guidance, see sections II.C.2, Postapproval Changes, and III.D, In Vitro Studies) to determine when changes in components, composition, and/or method of manufacture suggest that further in vitro and/or in vivo studies be performed.

2. Postapproval Changes

In the presence of certain major changes in components, composition, manufacturing site, and/or method of manufacture after approval, FDA recommends that in vivo BE be demonstrated for the drug product after the change in comparison to the drug product before the change. Under section 506A(c)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 356a(c)(2)), certain postapproval changes that require completion of studies must be submitted in a supplement and approved by FDA before distributing a drug product made with the change.

Information on the types of recommended in vitro dissolution and in vivo BE studies for immediate-release and modified-release drug products approved as NDAs for specified postapproval changes is provided in the following FDA guidances*:*

- *SUPAC-IR: Immediate Release Solid Oral Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Control; In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation*
- *SUPAC-MR: Modified Release Solid Oral Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation*

3. BE Considerations

BE studies are usually conducted using a crossover design. For such studies, intrasubject variability should be considered when determining the study sample size. In cases when a parallel design is necessary to evaluate BE, consideration should be given to total variability, including intersubject variability instead of just intrasubject variability.

A test product might fail to demonstrate bioequivalence because it has measures of rate and/or extent of absorption compared to the reference product outside acceptable higher or lower limits. For example, when the test product results in a systemic exposure that is significantly higher than that of the reference product, the concern is the typically limited experience from a safety standpoint for higher systemic concentrations. When the test product has a systemic exposure that is significantly lower than that of the reference product, the concern is potentially a lack of therapeutic efficacy of the test product. When the variability of the test product is greater than the reference product, the concern relates to both safety and efficacy, because it may suggest that the performance of the test product is not comparable to the reference product, and the test product may be too variable to be clinically useful.

When BE is not demonstrated, the sponsor should demonstrate that the differences in rate and extent of absorption do not significantly affect the safety and efficacy based on available dose-response or concentration-response data. In the absence of this evidence, failure to demonstrate BE may suggest that the test product should be reformulated, or the method of manufacture for the test product should be changed, or additional safety or efficacy data may be needed for the test product. In some cases, conclusions of BE based on the peak drug concentration (C_{max}) and area under the plasma concentration time curve (AUC) between the test product and the reference product may be insufficient to demonstrate that there is no difference in safety or efficacy if the systemic concentration-time profiles of the test product and the reference product are different (e.g., time to reach peak drug concentration (T_{max}) is different). For example, differences in the shape of the systemic concentration profile between the test and reference products could imply that the test product may not produce the same clinical response as the reference product. In such cases, additional data analysis (e.g., partial AUCs), exposure-response evaluation, or clinical studies may be recommended to evaluate the BE of the two products.

III. METHODS TO DOCUMENT BA AND BE

Under FDA's regulations, applicants must use the most accurate, sensitive, and reproducible method available to demonstrate BA or BE of a product (21 CFR 320.24(a)). As noted in 21 CFR 320.24, several in vivo and in vitro methods can be used to measure BA and to establish BE. These include, in general order of preference, pharmacokinetic (PK) studies, in vitro tests predictive of human in vivo BA (in vitro-in vivo correlation), pharmacodynamic (PD) studies, studies with clinical benefit endpoints, and other in vitro studies. In addition, where in vivo data are appropriate to demonstrate BA, our regulations provide guidelines on specific types of in vivo BA studies (see 21 CFR 320.25 through 320.29). This guidance predominantly focuses on the use of PK studies to document BA or BE.

A. Pharmacokinetic Studies

1. General Considerations

FDA's regulations generally define BA and BE in terms of rate and extent of absorption of the active ingredient or moiety to the site of action.[9] For in vivo studies, the regulations also provide for use of PK measures in an accessible biological matrix such as blood, plasma, and/or serum to indicate release of the drug substance from the drug product into the systemic circulation.[10] BA and BE frequently rely on PK measures such as AUC to assess extent of systemic exposure and C_{max} and T_{max} to assess rate of systemic absorption. PK-based comparisons to describe relative BA or make BE determinations are predicated on an understanding that measuring the active moiety or ingredient at the site of action is generally not possible and on an assumption that some relationship exists between the efficacy/safety and concentration of the active moiety and/or its important metabolite(s) in the systemic circulation. A typical study is conducted as a crossover study. The crossover design reduces variability caused by patient-specific factors, thereby increasing the ability to discern differences because of formulation.

2. Pilot Study

If the sponsor chooses, a pilot study in a small number of subjects can be carried out before proceeding with a full-scale BA or BE study. The pilot study can be used to validate analytical methodology, assess PK variability, determine sample size to achieve adequate power, optimize sample collection time intervals, and determine the length of the washout period needed between treatments. For example, for conventional immediate-release products, careful timing of initial samples may avoid a subsequent finding in a full-scale study that the first sample collection occurs after the C_{max}. For modified-release products, a pilot study can help determine the sampling schedule needed

[9] 21 CFR 320.1(a) and (e).

[10] See, e.g., 21 CFR 320.24(b)(1)(i). If serial measurements of the drug or its metabolites in plasma, serum, or blood cannot be accomplished, then measurement of urinary excretion can be used.

to assess lag time and dose dumping. The results of a pilot study can be used as the sole basis to document BA or BE provided the study's design and execution are suitable and a sufficient number of subjects have completed the study.

3. Full-Scale Study

General recommendations for a standard BA or BE study based on PK measurements are provided in Appendix A. Nonreplicate crossover study designs are recommended for BA and BE studies of immediate-release and modified-release dosage forms. However, sponsors and/or applicants have the option of using replicate designs for BE studies. Replicate crossover designs are used to allow estimation of (1) within-subject variance for the reference product, or for both the test and reference products, and (2) the subject by formulation interaction variance component. This design accounts for the inter-occasion variability that may confound the interpretation of a BE study as compared to a non-replicate crossover approach. The recommended method of analysis for nonreplicate or replicate studies to evaluate BE is average BE, as discussed in section IV. Recommendations for conducting and evaluating replicate study designs can be found in the FDA guidance for industry *Statistical Approaches to Establishing Bioequivalence.*

4. Study Population

Subjects recruited for BA or BE studies should be 18 years of age or older and capable of giving informed consent. In general, BA and BE studies should be conducted in healthy volunteers if the product can be safely administered to this population. A study in healthy volunteers is likely to produce less PK variability compared with that in patients with potentially confounding factors such as underlying and/or concomitant disease and concomitant medications. Male and female subjects should be enrolled in BA and BE studies unless there is a specific reason to exclude one sex. Such exclusions could be related to the drug product being indicated in only one sex or a greater potential for adverse reactions in one sex compared to the other. For example, oral contraceptives are evaluated in female subjects because the indication is specific to females. If a drug has the potential to be a teratogen, the drug product should be evaluated in male subjects. Female subjects enrolled in the study should not be pregnant at the beginning of the study and should not become pregnant during the study. In some instances (e.g., when safety considerations preclude use of healthy subjects), it may be necessary to evaluate BA and BE in patients for whom the drug product is intended. In this situation, sponsors and/or applicants should attempt to enroll patients whose disease process is expected to be stable for the duration of the study.

5. Single-Dose and Multiple-Dose (Steady State) Testing

This guidance generally recommends single-dose PK studies to assess BA and BE because they are generally more sensitive than steady-state studies in assessing rate and extent of release of the drug substance from the drug product into the systemic circulation.

FDA's regulations at 21 CFR 320.27 provide guidelines on the design of a multiple-dose in vivo BA study. This regulation also identifies instances in which multiple-dose BA studies may be required:

i. There is a difference in the rate of absorption but not in the extent of absorption.
ii. There is excessive variability in bioavailability from subject to subject.
iii. The concentration of the active drug ingredient or therapeutic moiety, or its metabolite(s), in the blood resulting from a single dose is too low for accurate determination by the analytical method.
iv. The drug product is an extended-release dosage form.[11]

We recommend that if a multiple-dose study design is performed, appropriate dosage administration and sampling be carried out to document attainment of steady state.

6. Bioanalytical Methodology

We recommend that sponsors ensure that bioanalytical methods for BA and BE studies be accurate, precise, specific, sensitive, and reproducible. A separate FDA guidance, *Bioanalytical Method Validation*, is available to assist sponsors in validating bioanalytical methods.[12]

7. Administration Under Fasted/Fed Conditions

The BA or BE study should be conducted under fasting conditions (after an overnight fast of at least 10 hours) except when tolerability issues are anticipated with fasting. In these cases, we recommend that applicants conduct only a fed study. A separate FDA guidance, *Food-Effect Bioavailability and Fed Bioequivalence Studies* is available to assist sponsors.

8. Moieties to Be Measured

The active ingredient that is released from the dosage form or its active moiety and, when appropriate, its active metabolites[13] should be measured in biological fluids collected in BA studies.

Measurement of the active ingredient or the active moiety, rather than metabolites, is generally recommended for BE studies because the concentration-time profile of the active ingredient or the active moiety is more sensitive to changes in formulation performance than that of the metabolite, which is more reflective of metabolite formation, distribution, and elimination. The following are instances when an active metabolite(s) should be measured.

[11] 21 CFR 320.27(a)(3).
[12] See also 21 CFR 320.29.
[13] See 21 CFR 320.24(b)(1)(i).

- Measurement of a metabolite(s) is necessary when the active ingredient or the active moiety concentrations are too low to allow reliable analytical measurement in blood, plasma, or serum. In this case, the metabolite should be measured in lieu of the active ingredient or active moiety. We recommend that the confidence interval approach be applied to the metabolite data obtained from these studies.

- Measurement of a metabolite(s) is necessary in addition to the active ingredient or active moiety if the metabolite is formed by presystemic metabolism and contributes meaningfully to efficacy and/or safety. The confidence interval approach should be used for all moieties measured. However, the BE criteria are only generally applied to the active ingredient or active moiety. Sponsors should contact the appropriate review division to determine which moieties should be measured.

9. Pharmacokinetic Measures of Systemic Exposure

This guidance recommends that systemic exposure measures be used to evaluate BA and BE. Exposure measures are defined relative to peak, partial, and total portions of the plasma, serum, or blood concentration-time profile, as describe here:

- Peak Exposure

We recommend that peak exposure be assessed by measuring the C_{max} obtained directly from the systemic drug concentration data without interpolation. The T_{max} can provide important information about the rate of absorption. The first point of a concentration-time curve based on blood and/or plasma measurements is sometimes the highest concentration, which raises a question about the measurement of true C_{max} because of insufficient early sampling times. A carefully conducted pilot study may help to avoid this problem. Collection of an early time point between 5 and 15 minutes after dosing followed by additional sample collections (e.g., two to five) in the first hour after dosing may be sufficient to assess early peak concentrations. If this sampling approach is followed, we consider the data to be adequate, even when the highest observed concentration occurs at the first time point.

- Total Exposure (Extent of Absorption)

For single-dose studies, we recommend that the measurement of total exposure be:

- Area under the plasma, serum, or blood concentration time curve from time zero to time t (AUC_{0-t}), where t is the last time point with a measurable concentration.

- Area under the plasma, serum, or blood concentration time curve from time zero to time infinity ($AUC_{0-\infty}$), where $AUC_{0-\infty} = AUC_{0-t} + C_t/\lambda_z$. C_t is the last measurable drug concentration and λ_z is the terminal or elimination rate constant calculated according to an appropriate method.

- For drugs with a long half-life, truncated AUC can be used (see section VII.D, Long-Half-Life Drugs).

For steady-state studies, we recommend that the measurement of total exposure be the area under the plasma, serum, or blood concentration time curve from time zero to time tau over a dosing interval at steady state ($AUC_{0\text{-}tau}$), where tau is the length of the dosing interval.

- Partial Exposure

For orally administered drug products, BA and BE can generally be demonstrated by measurements of peak and total exposure. For certain classes of drugs and under certain circumstances (e.g., to assess onset of an analgesic effect), an evaluation of the partial exposure could be used to support the performance of different formulations by providing further evidence of therapeutic effect. This guidance recommends the use of partial AUC as a partial exposure measure. The time to truncate the partial area should be related to a clinically relevant PD measure. We also recommend that sufficient quantifiable samples be collected to allow adequate estimation of the partial area. For questions on the suitability of the PD measure or use of partial exposure in general, we recommend that sponsors and/or applicants consult the appropriate review division.

10. Comparison of PK measures in BE studies

An equivalence approach is recommended for BE comparisons. The recommended approach relies on (1) a criterion to allow the comparison, (2) a confidence interval for the criterion, and (3) a BE limit. Log-transformation of exposure measures before statistical analysis is recommended. This guidance recommends use of an average BE criterion to compare systemic exposure measures for replicate and nonreplicate BE studies of both immediate- and modified-release products. For additional information on data analysis, refer to Appendix A and to the FDA guidance for industry on *Statistical Approaches to Establishing Bioequivalence.*

B. Other Approaches to Support BA/BE

In certain circumstances, other approaches are recommended to support a demonstration of BA/BE. Below are some general considerations regarding these other approaches. Sponsors should consult FDA's guidances for industry for additional information on these methods as well.[14]

1. In Vitro Tests Predictive of Human In Vivo BA

[14] See footnote 2.

In vitro-in vivo correlation (IVIVC) is an approach to describe the relationship between an in vitro attribute of a dosage form (e.g., the rate or extent of drug release) and a relevant in vivo response (e.g., plasma drug concentration or amount of drug absorbed). This model relationship facilitates the rational development and evaluation of extended-release dosage forms. Once an IVIVC is validated, the in vitro test serves as a surrogate for BA and/or BE testing, as well as a tool for formulation screening and setting of the dissolution/drug-release acceptance criteria.

Specifically, in vitro dissolution/drug-release characterization is encouraged for all extended-release product formulations investigated (including prototype formulations), particularly if in vivo absorption characteristics are being defined for the different product formulations. Such efforts may enable the establishment of an IVIVC. When an IVIVC or association is established (21 CFR 320.24(b)(1)(ii)), the in vitro test can serve not only as a quality control specification for the manufacturing process, but also as an indicator of how the product will perform in vivo.

Additional information on the development and validation of an IVIVC can be found in the FDA guidance for industry *Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations*.

2. Pharmacodynamic Studies

PD studies are not recommended for orally administered drug products when the drug is absorbed into systemic circulation and a PK approach can be used to assess systemic exposure and evaluate BA or BE. PK endpoints are preferred because they are generally the most accurate, sensitive, and reproducible approach. However, in instances where a PK endpoint is not possible, a well-justified PD endpoint can be used to demonstrate BA or BE.

3. Comparative Clinical Studies

Clinical endpoints can be used in limited circumstances, for example, for orally administered drug products when the measurement of the active ingredients or active moieties in an accessible biological fluid (PK approach) or PD approach is not possible. Because these circumstances do not occur very often, use of this approach is expected to be rare.

4. In Vitro Studies

Under certain circumstances, BA and BE can be evaluated using in vitro approaches (e.g., dissolution/drug-release testing) during the preapproval and postapproval phases (see 21 CFR 320.24(b)(5) and (6)). For example, orally administered drugs that are highly soluble and highly permeable, and for which

the drug product is rapidly dissolving, documentation of BE using an in vitro approach (dissolution/drug-release studies) may be appropriate based on the Biopharmaceutics Classification System.[15]

The following FDA guidances provide recommendations on the development of dissolution methodology, setting specifications, and the regulatory applications of dissolution testing:

- *Dissolution Testing of Immediate-Release Solid Oral Dosage Forms*
- *Extended-Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations*

In addition, we recommend that sponsors consult other FDA guidances for additional information on when in vitro data may be appropriate to demonstrate BA or BE of a product.

IV. DOCUMENTING BA AND BE FOR VARIOUS DOSAGE FORMS

This section summarizes the recommendations for documenting BA and BE studies based on the specific dosage forms and whether these evaluations occur preaapproval or postapproval.

A. Solutions and Other Solubilized Dosage Forms

For oral solutions, elixirs, syrups, tinctures, or other solubilized forms, in vivo BA and/or BE are generally self-evident and a requirement of in vivo data for a product may be waived (21 CFR 320.22(b)(3)). In such instances, the applicant would be deemed to have complied with and fulfilled any requirement for in vivo data.[16] Although a comparative study is not necessary, characterization of the pharmacokinetics of the drug is required (21 CFR 314.50(d)(3)). In addition, in vivo BE studies that compare different solution formulations are waived based on the assumptions that release of drug substance from the drug product is self-evident and that the solutions do not contain any excipients that significantly affect drug absorption. However, there are certain excipients that may alter the BA (e.g., sorbitol may reduce the BA of drugs, and vitamin E may enhance the BA) in amounts sometimes used in oral liquid dosage forms. In this case, evaluation of in vivo BA and/or BE may be required.

B. Immediate-Release Products

Included in this discussion are capsules, tablets (including conventional, buccal, chewable, orally disintegrating, and sublingual dosage forms), and suspensions.

[15] See the FDA guidance for industry on *Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System*. This document provides complementary information on the Biopharmaceutics Classification System (BCS).

[16] See 21 CFR 320.22(b)(3).

1. Preapproval Changes

For BA and BE studies, we recommend a single-dose, fasting study be performed. Under certain circumstances, multiple-dose BA studies (see section III.A.5) and/or food effect studies may be necessary (See the FDA guidance for industry *Food-Effect Bioavailability and Fed Bioequivalence).* Unconventional dosage forms (buccal, chewable, orally disintegrating, and sublingual dosage forms) should be administered according to intended label use/instructions. In addition, a BA study may be needed with the unconventional dosage form swallowed intact to assess the impact of accidental swallowing of the intact product. Sampling should adequately capture the T_{max} and C_{max} in addition to total exposure.

We recommend that in vitro dissolution be evaluated for all orally administered products. In vitro dissolution test conditions could be the same or different for unconventional compared to conventional dosage forms. If differences in dissolution data exist, they should be discussed with the appropriate review division.

2. Postapproval Changes

Information on the types of in vitro dissolution and in vivo BE studies needed for approved immediate-release drug products when postapproval changes are made is provided in an FDA guidance for industry entitled *SUPAC-IR: Immediate Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation*. We recommend that for postapproval changes, the in vitro or in vivo comparison be made between the post-change and pre-change products.

C. Modified-Release Products

Modified-release (MR) products include extended-release (controlled-release, sustained-release)[17] and delayed-release products.

Extended-release (ER) products are dosage forms that are designed to extend or prolong the release of active ingredient or active moiety from the drug product and may allow a reduction in dosing frequency as compared to when the drug is administered in an immediate-release (IR) dosage form. These drug products can be developed to reduce fluctuations in plasma concentrations when compared to an IR product. ER products can be capsules, tablets, granules, pellets, or suspensions.

Delayed-release (DR) drug products are dosage forms that release active ingredient or active moiety at a time later than immediately after administration (i.e., these drug products exhibit a lag time in quantifiable plasma concentrations). Typically, coatings (e.g., enteric coatings) are

[17] For the purpose of this guidance, the terms *extended*, *controlled*, and *sustained* are used interchangeably.

used to delay the release of the drug substance until the dosage form has passed through the acidic medium of the stomach. Generally, DR products are treated as IR products. However, if the DR product has complex release characteristics, the relevant review division should be contacted for additional guidance.

If the drug product is an ER product, the following recommendations apply.

1. Preapproval: BA and BE Studies

FDA's regulations at 21 CFR 320.25(f) address the purpose of a BA study for an extended-release product, which is to determine if certain delineated conditions are met.[18] This regulation also provides that "the reference material(s) for such a bioavailability study shall be chosen to permit an appropriate scientific evaluation of the extended release claims made for the drug product."[19] Appropriate reference products may include (1) a solution or suspension of the active drug ingredient or therapeutic moiety, (2) a currently marketed non-controlled-release drug product containing the same active drug ingredient or therapeutic moiety and administered according to the dosage recommendations in the labeling of the non-controlled release drug product, and (3) a currently marketed ER drug product subject to an approved full NDA containing the same active drug ingredient or therapeutic moiety and administered according to the dosage recommendations in the labeling of currently marketed ER product.[20]

In general, the PK profile of the ER product may not match that of the approved IR product (e.g., T_{max} is different) or, in some cases, to another ER product. In such a case, establishing similar PK profiles using C_{max} and AUC may not be sufficient to show that the ER product is bioequivalent to the IR product. Thus, additional safety or efficacy studies or PK/PD assessments may be recommended. This guidance recommends that the following BA studies and food effect BA studies be conducted for an ER drug product submitted as an NDA for the scenarios described below:

<u>New ER formulation comparison to an already-approved IR product</u>

- For drugs with linear pharmacokinetics over the therapeutic dose range: A fasting study should be conducted comparing the ER product administered as a single dose at the highest strength to the IR reference administered over the least common time interval to achieve equivalent total dose as for the ER product.[21] If

[18] 21 CFR 320.25(f)(1).
[19] 21 CFR 320.25(f)(2).
[20] 21 CFR 320.25(f)(2)(i), (ii), and (iv). We recommend that a sponsor seeking to use as a reference product "a currently marketed extended release drug product subject to an approved full new drug application containing the same active drug ingredient or therapeutic moiety and administered according to the dosage recommendations in the labeling proposed for the extended release drug product," under 21 CFR 320.25(f)(2)(iii), consult with the Agency before commencing such a study.
[21] For example, when a 150-milligram (mg) ER product administered once daily (QD) is being developed that gives an approved 50-mg IR reference product administered three times a day (TID) or a 75-mg product administered two times a day (BID), a comparison of the 150-mg ER product administered as a single dose could be compared to

for safety reasons the highest strength cannot be used, a lower strength may be acceptable.

- For drugs with nonlinear pharmacokinetics over the therapeutic dose range: At a minimum, a single dose of the highest and lowest strengths of the ER product should be compared to their corresponding IR references administered over the ER dosing interval. If the relative BA of intermediate ER strengths cannot be inferred based on the above studies, a single-dose fasting study for the intermediate strength(s) of the ER product should be compared to the corresponding IR reference administered over the ER dosing interval.

- When the ER strengths are not proportionally similar in composition, a single-dose fasting dosage strength equivalence assessment study[22] or a dosage strength proportionality study[23] for the ER product should be conducted.

- A single-dose food-effect study should be conducted on the highest ER strength (see the 2002 Food-Effect Guidance).

- A steady state study should be conducted on the highest strength of the ER product compared to an approved IR reference dosed to achieve equivalent total dose as for the ER product.

<u>New ER product (ER_{new}) comparison to an approved ER product (ER_{old}) with a different dosing interval (i.e., where ER_{new} and ER_{old} have unequal dosing intervals)</u>

- The recommendations are the same as outlined in the previous section (Development of a new ER formulation given an already approved IR product) except for the choice of the reference product. In this case, the reference product could be either the approved ER_{old} or IR product.

<u>New ER product (ER_{new}) comparison to an approved ER product (ER_{old}) with the same dosing interval</u>

- A single-dose fasting BE study on the highest strength of the ER_{new} product compared to the ER_{old} product. If ER_{new} and ER_{old} are of different strength, then

either the 50-mg IR reference product administered TID or 75-mg IR reference product administered BID. In this case, the least common time interval is 24 hours.

[22] If three strengths, 10, 25, and 50 mg, are being developed for a new ER dosage form, the dosage strength equivalence study should be conducted using 5×10 mg, 2×25 mg, and 1×50 mg to achieve constancy of dose.

[23] If three strengths, 10, 25, and 50 mg, are being developed for a new ER dosage form, the dosage strength proportionality study should be conducted using 1×10 mg, 1×25 mg, and 1×50 mg to achieve constancy of dose and the dosage strength proportionality study should be conducted using 1×10 mg, 1×25 mg, and 1×50 mg.

comparison of ER_{new} versus ER_{old} should be made based on dose using the highest strengths.

- A single-dose, food-effect study should be conducted on the highest ER_{new} strength.

- When the ER_{new} strengths are not proportionally similar in composition, a single-dose fasting dosage strength equivalence assessment study or a dosage strength proportionality study[24] for the ER_{new} product should be conducted.

- In some cases, BE between the new and old ER products may not be sufficient to ensure that there is no difference in safety or efficacy if the PK profiles of the two ER products do not match (e.g., T_{max} is different). Additional data analysis or clinical studies may be needed to ensure that the two products are clinically equivalent.

2. Postapproval Changes

Information on the types of in vitro dissolution and in vivo BE studies for ER drug products approved in the presence of specific postapproval changes are provided in an FDA guidance for industry *SUPAC-MR: Modified Release Solid Oral Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation*. We recommend that for postapproval changes, the in vitro or in vivo comparison be made between the post-change and pre-change products.

D. Batch Size

For pivotal BE studies, the test batch should be representative of the production batches. Therefore, the size of the test batch should be at least 10% of the planned production batch size, or a minimum of 100,000 units, whichever is larger.

V. ADDITIONAL INFORMATION ON IN VITRO APPROACHES

A. In Vitro Studies Conducted in Support of a Waiver of an In Vivo BA or BE Data Requirement

As discussed above, FDA's regulations contemplate that if in vivo BA or BE data are required for a product, a sponsor may seek a waiver of that requirement under certain circumstances.[25]

[24] 21 CFR 320.21(b) (giving applicants the option of submitting information that "would permit FDA to waive the submission of evidence demonstrating in vivo bioequivalence") and 320.21(f) (requiring that the information submitted in support of a waiver request "shall meet the criteria set forth in § 320.22").

[25] 21 CFR 320.21(b) (giving applicants the option of submitting information that "would permit FDA to waive the submission of evidence demonstrating in vivo bioequivalence") & 320.21(f) (requiring that the information submitted in support of a waiver request "shall meet the criteria set forth in § 320.22.")

For example, in some instances, in vivo BA or BE is self-evident based on certain characteristics of the drug product (21 CFR 320.22(b)), and therefore, any in vivo data requirement has been deemed to have been met. In other delineated circumstances, an in vivo BA or BE data requirement may be waived, and in vitro data may be accepted in lieu of in vivo data (21 CFR 320.22(d)). For example, an in vivo data requirement may be waived for different strengths of an immediate-release drug product under 21 CFR 320.22(d)(2) when (1) the drug product is in the same dosage form, but in a different strength; (2) this different strength is proportionally similar in its active and inactive ingredients to another drug product for which the same manufacturer has obtained approval; and (3) the new strength meets an appropriate in vitro test as outlined in the regulation.[26] In addition, for waiving higher strengths, linearity of the pharmacokinetics over the therapeutic dose range should be demonstrated.

This guidance defines *proportionally similar* in the following ways:

- All active and inactive ingredients are in exactly the same proportion between different strengths (e.g., a tablet of 50-mg strength has all the inactive ingredients, exactly half that of a tablet of 100-mg strength, and twice that of a tablet of 25-mg strength).

- For high-potency drug substances (where the amount of active drug substance in the dosage form is relatively low), (1) the total weight of the dosage form remains nearly the same for all strengths (within ± 10 % of the total weight of the strength on which a BE was performed), (2) the same inactive ingredients are used for all strengths, and (3) the change in any strength is obtained by altering the amount of the active ingredients and one or more of the inactive ingredients.

- Bilayer tablets are considered to be one formulation even though they consist of two separate layers with different compositions. In assessing the proportional similarity of the different strengths, all components of both layers should be proportionally similar. The fact that only one layer is proportionally similar and the other is not clearly indicates that the products (whole tablet) are not proportionally similar. This is relevant because there can be interactions between the different tablet layers, which can differ across different strengths because of the different size of the layers and the varying amounts of excipients present in each layer.

Exceptions to the above definitions may be possible if adequate justification is provided and discussed with the appropriate review division.

B. In Vitro Studies Conducted in Support of Demonstrating BA or BE

[26] See also 21 CFR 322.22(d)(3) and (4) for additional bases for waiver. Also, FDA, for good cause, may waive a requirement for the submission of evidence of in vivo bioavailability or bioequivalence if waiver is compatible with the protection of the public health. For full NDAs, FDA may defer a requirement for the submission of evidence of in vivo bioavailability if deferral is compatible with the protection of the public health (21 CFR 320.22(e)).

FDA may determine that in vitro data are the most accurate, sensitive, and reproducible method to demonstrate BA or BE in other contexts (21 CFR 320.24(b)(5) and (6)).[27] Below we provide additional guidance on the conduct of such studies.

1. Immediate-Release Formulations (Capsules, Tablets, and Suspensions)

In vitro data can be used to compare formulations of drug products under certain circumstances. If an applicant seeks to demonstrate the BA or BE of immediate-release formulations for capsules, tablets, and suspensions using in vitro data, FDA recommends that sponsors generate dissolution profiles for all strengths using an appropriate dissolution method. If the dissolution results indicate that the dissolution characteristics of the product are not dependent on the pH and product strength, dissolution profiles in one medium are usually sufficient to support demonstrating BE. Otherwise, dissolution data in at least three media (e.g., pH 1.2, 4.5, and 6.8) are recommended. The f_2 test should be used to compare profiles from the different strengths of the product (see FDA guidance for industry, *Dissolution Testing of Immediate Release Solid Oral Dosage Forms*). An f_2 value ≥ 50 indicates a sufficiently similar dissolution profile to support a biowaiver. For an f_2 value < 50, discussion with the appropriate review division is recommended to determine whether an in vivo study is needed. The f_2 approach is not suitable for rapidly dissolving drug products (e.g., $\geq$ 85% dissolved in 15 minutes or less).

- *Over-encapsulation of clinical trial formulations*

During the course of drug development, sponsors sometimes have to blind the formulations that they use in the clinical trials. In certain situations, the only difference between the to-be-marketed and clinical trial formulations is that the dosage form is put into a capsule. This over-encapsulation is done mainly for blinding purposes. It may be possible to support bioequivalence of the to-be-marketed and clinical trial formulations using in vitro data only, provided that no other excipients are added to the capsule and the dissolution profiles are comparable in three media: pH 1.2, pH 4.5 and pH 6.8.

- *Scale-up and postapproval changes*

Certain formulation changes in components and composition, scale-up, manufacturing site, manufacturing process, or equipment can be made postapproval. Depending on the possible impact of the manufacturing change on the release of the active ingredient from the formulation and its BA, certain manufacturing changes for IR products can be approved based solely on similarity of the dissolution profiles between the postchange and prechange formulations. Information on recommendations for using in vitro dissolution and in vivo BE studies for immediate-release drug products in such circumstances is provided in FDA's guidance for industry on *SUPAC IR: Immediate-Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing, and In Vivo Bioequivalence*

[27] In such instances, no waiver under 21 CFR 320.21 and 320.22 is necessary.

Documentation. The same principles described in the guidance can be applied to pre-approval changes in which the to-be-marketed formulation differs from the clinical trial formulation.

2. Modified-Release Formulations

The use of in vitro data may be acceptable for modified-release drug products for which specific postapproval changes are sought is delineated in the FDA guidance for industry *SUPAC-MR: Modified Release Solid Oral Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation.* The same principles described in the guidance may also apply to preapproval changes. Additional considerations for use of in vitro data are described below.

- *Beaded capsules: lower/higher strength*

For ER beaded capsules where the strength differs only in the number of beads containing the active moiety, a single-dose, fasting BA or BE study, as appropriate, should be carried out on the highest strength. In vivo BA or BE of one or more lower strengths can be demonstrated based on dissolution profile comparisons, with an in vivo BA or BE study only on the highest strength (unless safety reasons preclude the administration of the highest strength to healthy volunteers). The dissolution profiles for each strength should be generated using the recommended dissolution method. If the dissolution method has not been finalized, dissolution profiles should be generated in at least three media (e.g., pH 1.2, 4.5, and 6.8). In vivo BE studies for higher strengths may not be necessary based on (1) clinical safety and/or efficacy data on the proposed dose and the need for the higher strength, (2) linearity of pharmacokinetics over the therapeutic dose range, and (3) the same dissolution procedures being used for all strengths with similar dissolution results. The f_2 test can be used to demonstrate similar profiles among the different strengths of the product.

- *MR dosage forms: lower strength*

For MR dosage forms, when the drug product is in the same dosage form but in a different strength and when (1) the drug exhibits linear pharmacokinetics, (2) the various strengths are proportionally similar in their active and inactive ingredients[28] and (3) the drug-release mechanism is the same, an in vivo BA or BE determination of one or more lower strengths can be demonstrated based on dissolution profile comparisons, with an in vivo BA or BE study only on the highest strength. The dissolution profiles for each strength should be generated using the recommended dissolution method. If the dissolution method has not been finalized, dissolution profiles should be generated in at

[28] If the formulations of all the strengths are not compositionally proportional, in vitro data can be submitted for the middle strength(s) if the following data are acceptable: (1) BA or BE data, as appropriate, for both the highest and the lowest strengths, and (2) in vitro multimedia dissolution comparison profiles using f2 evaluation.

least three media (e.g., pH 1.2, pH 4.5, and pH 6.8). The dissolution profile should be generated on the test and reference products of all strengths using the same dissolution test conditions.

VI. SPECIAL TOPICS

A. Alcoholic Beverage Effects on MR Drug Products

The consumption of alcoholic beverages may affect the release of a drug substance from an MR formulation. The formulation may lose its MR characteristics, leading to more rapid drug release and altered systemic exposure. This more rapid drug release may have deleterious effects on the drug's safety and/or efficacy.

In vitro assessments of the drug release from the drug product using media with various alcohol concentrations should be conducted. Based on the results of the in vitro assessments, an in vivo BA study of the drug product when administered with alcohol may be needed.

B. Enantiomers versus Racemates

During development of a racemic drug product, the racemate should be measured in BA studies. It may also be important to measure the individual enantiomers of the racemate to characterize the pharmacokinetics of the enantiomers. For the development of a specific enantiomer, chiral inversion should be assessed.

Measurement of the racemate using an achiral assay is recommended for BE studies. Measurement of individual enantiomers in BE studies is recommended only when all of the following conditions are met: (1) the enantiomers exhibit different PD characteristics, (2) the enantiomers exhibit different PK characteristics, (3) primary efficacy and safety activity resides with the minor enantiomer, and (4) nonlinear absorption is present (as expressed by a change in the enantiomer concentration ratio with change in the input rate of the drug) for at least one of the enantiomers. In such cases, we recommend that BE criteria be applied to the enantiomers separately.

C. Drug Products With Complex Mixtures as the Active Ingredients

Certain drug products may contain complex drug substances (i.e., active moieties or active ingredients that are mixtures of multiple synthetic and/or natural source components). Some or all of the components of these complex drug substances may not be fully characterized with regard to chemical structure and/or biological activity. Quantification of all active or potentially active components in BA and BE studies may not be possible. In such cases, we recommend that BA and BE studies be based on a select number of components. Criteria for component selection typically include the amount of the moiety in the dosage form, plasma or blood levels of the moiety, and biological activity of the moiety. When PK approaches are infeasible to assess rate and extent of absorption of a drug substance from a drug product, PD, clinical, or in vitro approaches may be appropriate.

D. Long-Half-Life Drugs

In a BA or PK study involving an IR oral product with a long half-life (≥ 24 hours), adequate characterization of the half-life should include blood sampling over a long period of time. For BA or BE determination of a drug product containing a drug with a long half-life, a nonreplicate, single-dose, crossover study can be conducted, provided an adequate washout period is used. If the crossover study is problematic, a study with a parallel design can be used. For either a crossover or parallel study, we recommend that the sample collection time be adequate to ensure completion of gastrointestinal transit (approximately 2 to 3 days) of the drug product and absorption of the drug substance. C_{max} and a suitably truncated AUC can be used to characterize peak and total drug exposure, respectively. For drugs that demonstrate low intrasubject variability in distribution and clearance, a truncated AUC (e.g., $AUC_{0\text{-}72\ hr}$) can be used in place of $AUC_{0\text{-}t}$ or $AUC_{0\text{-}\infty}$. For drugs that demonstrate high intrasubject variability in distribution and clearance, AUC truncation should not be used. In such cases, we recommend that sponsors and/or applicants consult the appropriate review division.

E. Orally Administered Drugs Intended for Local Action

Documentation of BA and BE when the drug substance produces its effects by local action in the gastrointestinal tract can be achieved either by using pharmacokinetics, an acceptable PD end point, clinical efficacy and safety studies, and/or suitably designed and validated in vitro studies, as appropriate. For such cases, we recommend that sponsors and/or applicants consult the appropriate review division. Additional safety studies may also be recommended to characterize the local safety of the product. The in vitro studies should reflect important clinical effects or should be more sensitive to changes in product performance compared to a clinical study. To ensure comparable safety, additional studies with and without food may help to understand the degree of systemic exposure that occurs following administration of a drug product intended for local action in the gastrointestinal tract.

F. Combination/Coadministered Drug Products

Two or more active ingredients can be formulated as a single drug product, which is referred to as a combination drug product. Generally, the purpose of an in vivo BA study involving a combination drug product is to compare the rate and extent of absorption of each active drug ingredient or therapeutic moiety in the combination drug product to the rate and extent of absorption of each active drug ingredient or therapeutic moiety administered concurrently in separate single-ingredient preparations (21 CFR 320.25(g).

For the purpose of defining BA or determining BE when required, this guidance recommends that the following studies be conducted for a combination drug product:

- A two-treatment, single-dose, fasting study of the combination drug product versus single-ingredient drug products administered concurrently as a single treatment or an approved combination product containing the same active ingredients. This study should

use the highest strength of the combination product with matching doses of individual drug products.

- Certain alternative study designs may also be acceptable depending on the specific situation. For instance, in the case of a combination product consisting of two components, a three-treatment study design comparing the combination drug product versus single-ingredient drug products administered separately may be appropriate.

- A single-dose, food-effect study on the combination drug product.

BE studies for the combination product should include the measurement of systemic concentrations of each active ingredient. The confidence interval approach should be applied to each measured entity of the combination drug product and its reference product.

In specific cases, drug products are given in combination (not co-formulated) with the objective of increasing the exposure of one of the drugs (subject drug). The second drug is not intended to have a therapeutic effect and is given only to increase the systemic exposure of the subject drug. When both the subject and second drug are new molecular entities, the BA of each should be assessed separately. If a BE study is needed for the subject drug for any reason, the subject drug should be administered with the second drug for both test and reference products. The corresponding PK results, including confidence intervals for BE criteria, should be applied to the subject drug. It is not necessary to measure the concentrations of the second drug. BE studies that are needed for the second drug should be conducted only with the second drug; the subject drug is not dosed with the second drug. When the combination includes a new molecular entity and an approved product, only the BA of the new molecular entity should be assessed. It is assumed that the BA of the approved product has been previously evaluated.

G. Endogenous Substances

Drug products can be developed that contain compounds that are endogenous to humans (e.g., testosterone). When the endogenous compounds are identical to the drug that is being administered, determining the amount of drug released from the dosage form and absorbed by each subject is difficult. In most cases, it is important to measure and approximate the baseline endogenous levels of the compound in blood (plasma) and subtract these levels from the total concentrations measured from each subject after the drug product is administered. In this way, an estimate of actual drug availability from the drug product can be achieved, and therefore BA and BE can be assessed. Endogenous substances may have homeostatic processes that affect their production and therefore impact their systemic concentrations. To reduce the complication of these homeostatic processes and to potentially avoid the need for baseline correction, an alternative approach might be to enroll patients in BA and BE studies with low or no production of the endogenous substances instead of healthy volunteers.

Baseline concentrations of the endogenous substance produced by the body are measured in the time period prior to study drug administration. Depending on the proposed indication, subtraction of the time-averaged baseline or time-matched baseline from the post-dose

concentration for each subject may be recommended. When the endogenous levels are influenced by diet, strict control of the dietary intake of the compound prior to and during the study may also be appropriate. To achieve a stable baseline, subjects should be housed at the clinic for a sufficient time prior to the study and served standardized meals with similar content of the compound to that of the meals served on the PK sampling day.

In either case, baseline concentrations should be determined for each dosing period, and baseline corrections should be period-specific. If a negative plasma concentration value results after baseline correction, this should be set to 0 prior to calculating the baseline-corrected AUC. Pharmacokinetics and statistical analysis should be performed on both uncorrected and corrected data as appropriate. Because of the complexities associated with endogenous compounds, we recommend that sponsors and/or applicants contact the appropriate review division for additional guidance.

H. Drug Products With High Intrasubject Variability

In addition to the traditional approach and the use of average BE using replicate designs, the use of a reference-scaled BE approach using a replicate design can be considered. This approach should be reserved for drugs that demonstrate a high intrasubject variability (≥30%). The reference-scaled average BE approach adjusts the BE limits of highly variable drugs by scaling to the within-subject variability of the reference product in the study and imposes a limit of 0.8 to 1.25 on the geometric mean ratio.[29] The appropriate review division should be consulted when planning the use of the reference-scaled BE approach.

[29] For general principles of the reference-scaled approach, refer to Davit B, Conner D. Reference-Scaled Average Bioequivalence Approach. In: Kanfer I, Shargel L, Eds. *Generic Drug Product Development – International Regulatory Requirements For Bioequivalence.* Informa Healthcare, 2010:271-272.

APPENDIX A: GENERAL STUDY DESIGN AND DATA HANDLING

The following general approaches are recommended, recognizing that the elements can be adjusted for certain drug substances and drug products.

Study conduct

- The BA or BE study should be conducted under fasting conditions (after an overnight fast of at least 10 hours). If the BA or BE study needs to be conducted with food, a separate FDA guidance *Food-Effect Bioavailability and Fed Bioequivalence Studies* is available to assist sponsors.

- The test and reference products should be administered with about 8 ounces (240 milliliters) of water to an appropriate number of subjects.

- Generally, the highest marketed strength should be administered as a single unit. If warranted, to achieve sufficient bioanalytical sensitivity multiple units of the highest strength can be administered, provided the total single dose remains within the labeled dose range and the total dose is safe for administration to the study subjects.

- An adequate washout period (e.g., ≥5 half-lives of the moieties to be measured) should separate each treatment.

- The lot numbers of both test and reference listed products and the expiration date for the reference product should be stated. We recommend that the assayed drug content of the test product batch not differ from the reference product by more than +/- 5 percent. The sponsor should include a statement of the composition of the test product and, if possible, a side-by-side comparison of the compositions of test and reference listed products. In accordance with 21 CFR 320.38, and 21 CFR 320.63, samples of the test and reference listed product must be retained for at least 5 years. For additional information, please refer to the FDA guidance for industry on *Handling and Retention of Bioavailability and Bioequivalence Testing Samples.*

- Before and during each study phase, we recommend that subjects (1) be allowed water as desired except for 1 hour before and after drug administration, (2) be provided standard meals no less than 4 hours after drug administration, and (3) abstain from alcohol for 24 hours before each study period and until after the last sample from each period is collected.

Sample collection and sampling times

- We recommend that under normal circumstances, blood, rather than urine or tissue, be used. In most cases, drug or metabolites are measured in serum or plasma. However, in certain cases, such as when an assay of sufficient sensitivity cannot be developed for plasma, whole blood may be more appropriate for analysis. We recommend that blood samples be drawn at

appropriate times to describe the absorption, distribution, and elimination phases of the drug. For most drugs we recommend that 12 to 18 samples, including a pre-dose sample, be collected per subject per dose. ***This sampling should continue for at least three or more terminal elimination half-lives of the drug*** to capture 90 percent of the relevant AUC. For multiple-dose studies, sampling should occur across the dose interval and include the beginning and the end of the interval. The exact timing for sample collection depends on the nature of the drug and the rate of input from the administered dosage form. The sample collection should be spaced in such a way that the maximum concentration (C_{max}) of the drug in the blood and terminal elimination rate constant (λ_Z) can be estimated accurately.

Three or more samples should be obtained during the terminal log-linear phase to obtain an accurate estimate of λ_z from linear regression. We recommend recording the actual clock time when samples are drawn, as well as the elapsed time related to drug administration.

Subjects with pre-dose plasma concentrations

- If the pre-dose concentration is ≤ 5 percent of C_{max} value in that subject, the subject's data without any adjustments can be included in all PK measurements and calculations. We recommend that if the pre-dose value is > 5 percent of C_{max}, the subject should be dropped from all PK evaluations. The subject data should be reported and the subject should be included in safety evaluations.

Data deletion because of vomiting

- We recommend that data from subjects who experience emesis during the course of a study for immediate-release products be deleted from statistical analysis if vomiting occurs at or before 2 times median T_{max}. For modified-release products, subjects who experience emesis at any time during the labeled dosing interval should not be included in PK analysis.

Data submission and analysis

The following PK information is recommended for submission:

- Plasma concentrations and time points.
- Subject, period, sequence, treatment.
- Intersubject, intrasubject, and/or total variability, if available.
- For single-dose studies: $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, C_{max}, T_{max}, λ_z, and $t_{1/2}$.
- For steady-state studies: $AUC_{0\text{-}tau}$, C_{maxss}, T_{max}, C_{minss} (lowest concentration in a dosing interval), C_{trough} (concentration at the end of the dosing interval), C_{avss} (average concentration during a dosing interval), degree of fluctuation $[(C_{max}\text{-}C_{min})/C_{avss}]$, swing $[(C_{maxss}\text{-}C_{minss})/C_{minss}]$. C_{trough} should be measured for several dosing intervals to assess whether steady-state was achieved.

- In addition to the above information, clearance and volume of distribution should be reported for BA studies.

In addition, we recommend that the following statistical information be provided for AUC_{0-t}, $AUC_{0-\infty}$, and C_{max}:

- Geometric means
- Arithmetic means
- Geometric mean ratios
- 90 percent Confidence intervals (CI)

We also recommend that logarithmic transformation be provided for measures used for BE demonstration. An FDA guidance for industry, *Statistical Approaches to Establishing Bioequivalence*, is available.

Rounding off of confidence interval values

We recommend that applicants ***not round off*** CI values; therefore, to pass a CI limit of 80 to 125 percent, the value should be at least 80.00 percent and not more than 125.00 percent.

M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: July 29, 2015

To: Sharon Hertz, M.D., Director
Division of Anesthesia, Analgesia, and Addiction Products

Through: Michael Klein, Ph.D., Director
Controlled Substance Staff

From: James M. Tolliver, Ph.D., Pharmacologist
Silvia Calderon, Ph.D., Pharmacologist
Controlled Substance Staff

Subject: OPEN SESSION BACKGROUND DOCUMENT on In Vitro Physical Manipulation Studies and Intranasal Human Abuse Potential Study OCI1005 Submitted Under NDA 206-830. Prepared for the FDA Joint Meeting of the Anesthetic and Life Support Drugs and Drug Safety & Risk Management Advisory Committees, September 10, 2015.

Background

The following is a summary of the review conducted by the Controlled Substance Staff on the characterization of the abuse deterrent properties of Avridi, immediate-release oxycodone hydrochloride tablets (OCI tablets), developed by Purdue Pharma L.P. (the Sponsor) under NDA 206-830.

Avridi, immediate-release oxycodone hydrochloride tablets (5 mg, 10 mg, 15 mg, 20 mg and 30 mg), is formulated with a combination of gelling agents intended to mitigate intravenous abuse, and an aversive agent intended to mitigate intranasal abuse. The OCI tablets are not formulated to resist crushing.

The Sponsor conducted premarketing studies, to characterize the abuse-deterrent properties of the formulation, as delineated in the FDA Guidance for Industry: Abuse Deterrent Opioids-Evaluation and Labeling[1]

[1] . FDA/ CDER. Final Guidance for Industry: Abuse Deterrent Opioids- Evaluation and Labeling, 2015 http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM334743.pdf

Premarketing studies consist of in vitro manipulation studies, pharmacokinetic studies and human abuse potential studies.

The next sections will discuss findings and provide conclusions from in vitro studies and an intranasal human abuse potential study.

In vitro Manipulation Studies

In vitro studies were conducted to evaluate the ease with which the abuse deterrent properties of OCI tablets could be defeated or compromised by physicochemical processes. These studies were designed to simulate common methods of manipulation, as well as more complex methods of extraction, that may illustrate the separation or inactivation of the aversive irritant agent present in the product. Physical manipulation studies were conducted with the goal of reducing the formulation to a powder to be used in extraction studies, and that could be abused intranasally. Additional studies explored the feasibility of obtaining a solution for injection (syringeability studies) using OCI tablets and the positive comparator. Vaporization studies examined the feasibility of using crushed OCI tablets for abuse by smoking.

In vitro studies were designed by the Sponsor in consultation with experts and many of the studies were conducted by a third party. The studies employed a bracket approach by analyzing the lowest and the highest tablet strengths (5 mg and 30 mg). Considering that all strengths are qualitatively and quantitatively proportional, the analyzed strengths represent the behavior of all proposed strengths.

The positive control used in these studies was commercially available immediate release oxycodone 30 mg tablets. When needed the free base or the hydrochloride (HCl) salt of oxycodone, and the irritant substance included in the formulation were used as controls to validate specific procedures.

Protocols included sufficient replicates for evaluation of method variability. The studies were designed to assess a range of conditions that can defeat the abuse deterrent characteristics of the formulation by using a wide range of chemical and physical conditions, temperatures, and extraction times.

Conclusions Regarding In Vitro Studies

Based on the review of the data provided by the Sponsor from physical manipulation, tablet pretreatment studies, extraction studies using water and other solvents, attempts to extract oxycodone in its free base form, syringeability, and smoking studies, CSS concluded that:

1. In vitro studies demonstrate overall that OCI tablets have properties that make product manipulation difficult for purposes of intravenous or intranasal abuse.

2. Physical manipulation studies showed that OCI tablets and the immediate release comparator tablets (positive control) were easily ground to a powder. Particle size of the powder was suitable for intranasal administration, regardless of tools used.

Physical manipulation studies were conducted to determine the optimal grinding conditions needed to generate a homogeneous blend of crushed OCI tablet material that could be studied in the intranasal human abuse potential studies and in extraction studies.

3. In the tablet pretreatment study of intact tablets, recovery of oxycodone HCl and irritant decreased with certain experimental conditions, indicating some degradation of both substances. Selective degradation of the irritant over oxycodone hydrochloride was observed under some specific treatment conditions.

   Experiments were conducted to assess the impact of various tablet pretreatments on the recoverable amounts of oxycodone HCl and the irritant agent, and to understand the potential for selective degradation of the irritant.

4. Extraction studies showed that the recovery of oxycodone HCl and irritant from intact and ground OCI tablets was generally rapid and efficient with a variety of solvents, and increased with temperature.

   Extraction studies were performed to determine the amount of oxycodone HCl and irritant agent that could be obtained from intact or crushed tablets using a variety of extraction conditions (time, temperature, particle size and solvent polarity), and to determine the potential for the preferential separation of the irritant agent under the conditions tested.

5. Under most extraction conditions tested, both the irritant and oxycodone HCl were extracted, indicating that the tested conditions did not successfully separate oxycodone from the irritant.

6. Multistep extraction studies showed that it was possible to extract oxycodone base under certain experimental conditions. However, depending upon the nature of the solvent, both irritant and excipients were also present in the residue.

   Multistep extraction studies were conducted to determine the extractability and solubility of oxycodone hydrochloride, oxycodone base and the irritant agent, and to determine the feasibility of preferentially separating oxycodone from the irritant agent present in the formulation.

7. Syringeability studies showed that it was difficult to prepare a solution suitable for intravenous injection using OCI tablets, under various experimental conditions, due to the gelling properties of the formulation and the size of the tablet. Depending on the volume of water used for extraction, either small volumes of aqueous solution too viscous to be injected or diluted solutions of oxycodone HCl of relatively high viscosity were obtained. In contrast, a solution suitable for injection was easily obtained using the currently available immediate release tablets used as a comparator in these studies.

8. In smoking studies, under the conditions studied by the Sponsor, OCI as well as the positive comparator were found not susceptible to abuse via smoking.

Study OCI1005 entitled "A Single-Center, Randomized, Double-Blind Crossover Study to Evaluate the Abuse Potential, Pharmacokinetics, and Safety of Crushed and Intranasally Administered Immediate Release Oxycodone (OCI) Tablets in Recreational Opioid Users."

The Sponsor conducted a human abuse potential study (Study OCI1005) to evaluate the abuse potential of manipulated OCI relative to manipulated commercially available immediate release (IR) oxycodone containing tablets, when abused via the intranasal route. This type of study is thought to be predictive of the likelihood that the new formulation with abuse deterrent properties will deter or reduce the abuse of the product when taken through common routes of abuse.

Description of Study

Study OCI1005 is a single-center, double-blind, double-dummy, placebo- and active-controlled, randomized 4-way crossover study consisting of the following four phases: screening, qualification, treatment, and follow-up. The positive comparator consisted of a commercially available immediate release (IR) oxycodone product formulated as a tablet.

The primary objective of the study was to evaluate the abuse potential and pharmacodynamic effects of intranasally administered crushed OCI tablets compared to crushed IR oxycodone tablet and placebo in 34 (Per Protocol Population) recreational opioid users with a history of intranasal abuse.

During the qualification phase, subjects self-administered crushed Roxicodone and placebo intranasally on day 1 and day 2 in a randomized crossover manner. In order to be eligible for the Treatment Phase, subjects were required to differentiate between the commercially available IR oxycodone product and placebo using selected subjective measures including, but not limited to, Drug Liking VAS.

The treatment phase consisted of a single visit (visit 4) lasting 13 days with 12 overnight stays. Subjects were administered 4 treatments (1 treatment per treatment period) in a double-blind, double-dummy (intranasal and oral), randomized sequence based on a 4x4 Williams square:

- OCI tablet, crushed intranasal
- IR Oxycodone tablet, crushed intranasal
- OCI 30 mg tablet, intact oral
- Placebo

For determining oxycodone pharmacokinetics, blood samples were collected pre-dose and at selected time intervals out to 24 hours post-dosing. Pharmacokinetic parameters determined for oxycodone included but were not limited to:

- C_{max} – Maximum plasma concentration
- T_{max} – Time to reach maximum plasma concentration
- $AUC_{0\text{-}3hr}$ – Area under the plasma concentration vs time curve (AUC) from time 0 to 3 hours post-dose, reflecting exposure to oxycodone during this time interval.

- AUC_{inf} – AUC extrapolated to infinity, reflecting total exposure to oxycodone.

Pharmacodynamic measures were assessed at selected time internals following dosing. Primary measures included visual analog scales (VAS) for Drug Liking, Overall Drug Liking, and Take Drug Again. High VAS was a secondary measure. Descriptions of these scales include:

- Drug Liking VAS - Subjects were asked the question "Do you like the effect that you are feeling now?" The question was scored using a 0-100 mm bipolar VAS anchored on the left with "strong disliking" (score of 0); "neither like nor dislike" (score of 50) in the middle; and anchored on the right with "strong liking" (score of 100).
- Unipolar High VAS - Subjects were asked the question "How high are you now?" Subjects were required to mark a vertical line on a unipolar 0-100 mm VAS anchored on the left by "none" (score of 0) and on the right by "extremely" (score of 100).
- Overall Drug Liking VAS – Subjects were asked "Overall, liking for this drug is:" The question was scored using a 0-100 mm bipolar VAS anchored on the left by "Strong Disliking", in the middle by "Neither Like nor Dislike, and on the right by "Strong Liking."
- Bipolar Take Drug Again VAS - Subjects were asked the question, "Would you want to take the drug you just received again, if given the opportunity?" The question was scored using a 0-100 mm bipolar VAS anchored on the left with "definitely would not" (score of 0); "do not care" (score of 50) in the middle; and anchored on the right with "definitely would" (score of 100).

Parameters determined for Drug Liking VAS included maximum effect (E_{max}), minimum effect (E_{min}), time to E_{max} or E_{min} (TE_{max} or TE_{min}), area under the effect curve (AUE) and AUE curve from time zero to 3 hours post-dosing. E_{max} was determined for Overall Drug Liking and Take Drug Again VAS.

Subject-rated assessment of nasal irritation was assessed at selected intervals post-dosing using a 100-point VAS (0 = "Not at all" to 100 = "Extremely"). Observations were based on 6 categories: Burning; Need to blow nose; Runny nose / nasal discharge; Facial pain/pressure; Nasal congestion; and Throat irritation.

<u>Conclusions Regarding Study OCI1005</u>

1. OCI tablets, but not commercially available IR oxycodone tablets serving as positive control, displayed potential deterrent effects to intranasal abuse. As determined using the Drug Liking VAS, intranasal OCI produced a maximum level of drug liking above placebo but well below that of IR oxycodone administered intranasally. At the end of the dosing session, using the Overall Drug Liking VAS, subjects documented their overall drug liking experience as low following intranasal crushed OCI, as compared to following IR oxycodone intranasal. On the Take Drug Again VAS, subjects noted that they were not willing to take OCI crushed intranasally again but were willing to take IR oxycodone intranasally again, if given the opportunity.

2. Following intranasal administration of crushed OCI tablets, subjects administered the "High" VAS, reported a maximum feeling of high (euphoria) that was close to but statistically

significantly lower than the high produced by intranasal crushed IR oxycodone significantly above that following intranasal placebo. So, although subjects appear not to have liked the experience of intranasally administering crushed OCI tablets, they nevertheless perceived a significant euphoric effect (high).

3. The potential deterrent effect of OCI tablets to intranasal abuse is not due to reduced bioavailability of oxycodone from intranasally administered crushed OCI tablets compared to crushed IR oxycodone tablets administered. Intranasal administration of crushed OCI or crushed IR oxycodone results in similar maximum plasma concentrations of oxycodone (Cmax) and total oxycodone exposure over the first three hours as evidenced by similar areas under the plasma oxycodone concentration versus time curves ($AUC_{0\text{-}3hrs}$). This similarity in bioavailability of oxycodone may explain the significant levels of "high" reported by subjects following intranasal administration of either crushed OCI or crushed IR oxycodone tablets.

4. The potential deterrent effect of OCI tablets to intranasal abuse appears to be due to adverse nasal effects experienced following intranasal administration of crushed OCI tablets. Results of the Subject Rated Assessments of Irritation VAS subscales demonstrate that crushed OCI tablets given intranasally, but not placebo or crushed IR oxycodone tables given intranasally, produced within 10 - 15 minutes post-dosing significant levels of "burning" in the nasal cavity, "need to blow nose", "runny nose/nasal discharge", facial pain/pressure, nasal congestion and throat irritation. The presence of these symptoms coincided with minimum drug liking observed with a median time of about 9 minutes.

5. Results of Study OCI1005 demonstrate that intact OCI tablets may be abused orally. There is no evidence of a potential deterrent effect to oral abuse. Subjects taking intact OCI tablets reported significant levels of "drug liking" and "high" on the measures of Drug Liking VAS and High VAS, respectively. This was further supported by a favorable overall assessment of drug liking, as determined in the global balance of effects measure of Overall Drug Liking VAS. As evidenced from the Take Drug Again VAS, subjects were willing to take intact OCI tablets again, if given the opportunity.

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology Review (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Memorandum

To:	Ellen Fields, MD Sharon Hertz, MD Division of Anesthesia, Analgesia, and Addiction Products
From:	Jana McAninch, MD, MPH, MS Division of Epidemiology II
Through:	Cynthia Kornegay, PhD Team Leader, Division of Epidemiology II
	Judy Staffa, PhD, RPh Director, Division of Epidemiology II
Date:	July 20, 2015
Drug Name(s):	IR oxycodone with abuse-deterrent properties
Subject:	DEPI section for AC Background Packages: Ability of PMRs to assess adverse outcomes associated with food effects
Application Type/Number:	NDA 206830
Applicant/sponsor:	Purdue Pharma LLC
OSE RCM #:	2015-2547

Background:

On September 10, 2015, the Drug Safety and Risk Management and the Anesthetic and Analgesic Drug Products Advisory Committees will be convening to discuss an NDA for an immediate-release oxycodone product (NDA 206830) containing technology intended to deter abuse. Pharmacokinetic data for this product demonstrated significant food effects associated with the abuse-deterrent formulation. Pharmacokinetic studies demonstrated that oxycodone release and absorption are delayed significantly following administration with food, which will delay onset of action for pain relief.

The committees will be asked to discuss the potential safety risks and the potential effects on efficacy associated with the extent of these food effects, and potential fluctuations in oxycodone levels that may occur if this product is not taken consistently in the fasting state. These risks include the potential for an increased incidence of overdose due to the delayed onset of analgesic effect leading to patients taking repeated doses that could result in respiratory depression. The committee will also be asked to consider whether potential benefits to the public from abuse-deterrent properties outweigh the potential risks to patients from the food effects. Finally, the committee will vote on whether this drug should be approved for marketing in the U.S.

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) consulted the Division of Epidemiology II (DEPI) regarding the ability of postmarketing studies, and Postmarketing Requirements (PMRs), to assess the impact of this food effect. Specifically, DAAAP asked DEPI to submit a brief memo with language to be included in the Background Package for this advisory committee meeting discussing whether a PMR will be capable of evaluating the impact of the demonstrated food effect on patient outcomes in post-approval settings.

For inclusion in the Background Materials for NDA 206830—Overview of Risk Mitigation Strategies:

Postmarketing Requirements (PMRs):

Section 505(o)(3) of the Food Drug and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies or clinical trials for any or all of three purposes:[1]

1. To assess a known serious risk related to the use of the drug,
2. To assess signals of serious risk related to the use of the drug,
3. To identify an unexpected serious risk when available data indicates the potential for a serious risk.

[1] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/

All application holders of approved extended-release/long-acting (ER/LA) opioid analgesics are currently required to participate in conducting a suite of postmarketing observational studies with the overarching goal of quantitatively assessing the serious risks of misuse, abuse, addiction, overdose, and death associated with long-term use of opioid analgesics for management of chronic pain, as well as to conduct a postmarketing clinical trial assessing the risk of hyperalgesia associated with these drugs.[2] In addition, approved opioid analgesics formulated with properties intended to deter abuse are subject to individual PMRs requiring epidemiologic investigations to assess whether the properties intended to deter misuse and abuse of the product actually result in a meaningful decrease in misuse and abuse, and their consequences, addiction, overdose, and death in post-approval settings.

Opioid analgesic application holders have proposed and utilized a variety of data sources to fulfill these PMRs, including both traditional pharmacoepidemiologic data sources, such as administrative claims and electronic medical records, and non-traditional sources such as surveys and poison control center call data. FDA is unaware of any existing data source capable of monitoring patient adherence to dosing-related dietary instructions or assessing the incidence of adverse outcomes resulting from the significant food effect observed in pre-marketing trials.

In general, currently available data sources cannot reliably estimate the incidence of overdose and death associated with specific oxycodone products and formulations, and the only conceivable approach to assessing the impact of this food effect in post-approval settings would consist of primary data collection. Such a study would require detailed measurement of drug and dietary intake as well as patient-reported outcomes such as analgesic effect. In addition, the study would need to be powered to assess the incidence of rare outcomes, including overdose and death. A study with such detailed primary data collection that is also large enough to measure uncommon but serious outcomes with acceptable precision would likely be infeasible.

In summary, postmarketing epidemiologic studies will not be a practical means to assess the risk of adverse patient outcomes associated with food effects in post-approval settings. Nor will such studies be capable of evaluating the overall balance of risks and benefits attributable to this oxycodone product's abuse-deterrent properties and associated food effects.

[2] http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM367697.pdf

MEMORANDUM

MEDICATION ERROR REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	July 31, 2015
Requesting Office or Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 206830
Product Name and Strength:	Purdue Pharma's oxycodone hydrochloride immediate-release tablets 5 mg, 10 mg, 15 mg, 20 mg, 30 mg
Product Type:	Single ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Purdue Pharma L.P.
Submission Date:	August 29, 2014
OSE RCM #:	2015-1455
DMEPA Primary Reviewer:	Millie Shah, PharmD, BCPS
DMEPA Acting Team Leader:	Vicky Borders-Hemphill, PharmD
DMEPA Associate Director:	Irene Chan, PharmD, BCPS
DMEPA Director:	Todd Bridges, RPh

1 PURPOSE OF MEMO

In preparation for an upcoming Advisory Committee meeting, the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) consulted us to assess the risk of administration errors with Purdue Pharma's immediate-release oxycodone product should it be approved for marketing. Based on the pharmacokinetic profile of this product, it must be taken on an empty stomach, at least one hour prior to or two hours after eating. The requirement for the proposed product to be administered on an empty stomach is different from the currently available oxycodone hydrochloride immediate-release products that do not have a significant food effect to warrant a dietary restriction around taking the medication as needed (usually every 4 to 6 hours).[1]

2 ANALYSIS AND DISCUSSION

Purdue Pharma's immediate-release oxycodone product is a Schedule II immediate-release tablet formulation of oxycodone hydrochloride with abuse-deterrent properties. This filing is a 505(b)(2) application that references Roxicodone (oxycodone hydrochloride tablets USP). The Sponsor is seeking FDA approval for the indication of management of acute and chronic moderate to severe pain where use of an opioid analgesic is appropriate. The initial recommended dose of the proposed product is 5 mg to 15 mg orally every 4 to 6 hours as needed for pain. The incorrect administration of the proposed product with food would be expected to result in a decrease in Cmax and delay in Tmax, which may result in delay of onset of action for pain relief. When compared to Roxicodone, mean Cmax was 29.79 ng/mL and 41.43 ng/mL for the proposed product and Roxicodone under the fed condition, respectively. This indicates a 27% lower Cmax for the proposed product than the referenced drug in the presence of food. Additionally, under fed conditions, the median time to peak exposure (Tmax) was approximately 4 hours (Range: 1 to 9 hours) for the proposed product and approximately 1.5 hours (Range: 0.5 to 4 hours) for Roxicodone.[2] If the proposed product is administered in error with food, the resultant decrease in Cmax and delay in Tmax with the proposed product under fed conditions may have a detrimental effect on pain control.

The dosing interval for the proposed product is every 4 to 6 hours as needed. This frequency of administration requires multiple administrations of the drug throughout the day. Therefore, in our view, it seems impractical that the administration of the proposed product on an empty stomach could be routinely adhered to, especially for those patients that require an every four-hour dosing schedule. This dosage regimen requires careful timing of food ingestion with respect to administration of the medication, and the complicated nature of managing this regimen is prone to confusion and error. Appropriate administration of the proposed product requires the patient to take a dose either one hour prior to or two hours after eating. For those patients using a four-hour dosing interval, this leaves a one-hour window for the patient to consume food.

[1] Clinical Pharmacology Review. Submitted in DARRTS on June 4, 2015. Accessed on June 24, 2015.

[2] Clinical Pharmacology Review. Submitted in DARRTS on June 4, 2015. Accessed on June 24, 2015.

Table 1 below provides a depiction of the window of time a patient would have to consume food, while adhering to the four-hour dosing interval. If a patient takes a dose of the proposed product within the timeframe depicted by the red-shaded area in the table, the result will be a food effect with clinical consequences that include inadequate pain relief.

Table 1: Example timing of the proposed product dose and eating opportunities for a patient on a 4 hour dosing schedule

Time	Dose	Food
06:00	First dose-1 hour prior to eating	
07:00		Eat
08:00		
09:00		
10:00	Next dose: 4 hours after first dose	
11:00		Eat
12:00		
13:00		
14:00	Next dose: 4 hours after previous dose	

We recognize there are other medications that should be taken on an empty stomach that are currently marketed. However, the other drugs we are aware of with this administration requirement have dosing intervals that are less frequent than the 4 to 6 hour dosing interval for Purdue Pharma's immediate-release oxycodone hydrochloride tablet, which makes administration of these medications on an empty stomach more practical and reasonable to adhere to.

Strategies, including patient counselling by healthcare providers and label/labeling statements on the proposed product, to communicate appropriate administration in relation to food will help to minimize the risk for medication error, but are unlikely to address the practical aspects of administering this product on an empty stomach. Packaging strategies such as unit-dose packaging with clear instructions and cautionary directions to take on an empty stomach do not sufficiently mitigate the risk for administration errors because the dosing interval is so frequent. In our judgment, even if a patient understands that the product should be administered on an empty stomach, the frequency of administration of the product makes it unlikely that patients would be able to take this medication on an empty stomach consistently. Therefore, regardless of the robustness of patient counseling, packaging, and/or label/labeling statements, administration errors are still likely to occur.

Lastly, our analysis of the complex administration of this product identified other potential risks of errors. First, due to the narrow window during which patients may appropriately consume food, the complexity of administering other medications that should be administered with meals becomes even more difficult for patients on concurrent therapies with Purdue Pharma's immediate-release oxycodone hydrochloride tablet. Secondly, inadequate pain relief may potentiate additional medication errors if patients, attempting to achieve pain relief, take additional doses of the proposed product outside of the label-recommended dosing interval, which may result in an overdose of an opioid.

3 CONCLUSION

Due to the every 4 to 6 hour dosing interval and requirement to administer Purdue Pharma's immediate-release oxycodone hydrochloride tablet on an empty stomach, wrong administration medication errors are likely to occur, which may result in inadequate pain relief. Patient counseling by healthcare providers, packaging, and/or label/labeling strategies to communicate appropriate administration of the proposed product in relation to food will not likely be sufficient to prevent wrong administration medication errors due to the complexity of timing meals within a narrow window given the frequency of administration.